ECONOMIC EVALUATION OF THE COSTS AND COST-EFFECTIVENESS OF THE DIARRHEA ALLEVIATION THROUGH ZINC AND ORAL REHYDRATION THERAPY PROGRAM AT SCALE IN GUJARAT, INDIA

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Abstract

Problem: Diarrhea is the fourth leading killer of children under 5 worldwide, with India bearing the largest national burden. Effective and low-cost treatment is available through oral rehydration salts and zinc supplementation, and trial based literature suggests that these interventions are cost-effective. However, coverage of these interventions remains low, and strategies are being developed for scaling them up. It is less certain whether this health systems strategy is cost-effective at scale, or what economic impact it will have on caregivers. This dissertation evaluates the Diarrhea Alleviation through Zinc and ORS Treatment (DAZT) program in rural Gujarat India in terms of impact on caregiver costs, cost-effectiveness, and cost-effectiveness of different bundles of diarrhea and pneumonia prevention and treatment interventions.

Methods: The influence of factors on the odds and amount of economic costs to caregivers was evaluated with a two-part model. Due to the uncontrolled non-randomized study design, a net-benefit regression approach was used to evaluate cost-effectiveness while controlling for covariates. Cost-effectiveness of bundled services was evaluated with a mathematical model using probabilistic sensitivity analysis to evaluate uncertainty, and the Lives Saved Tool to project the number of deaths averted over five years.

Results: The DAZT program was not associated with a change in odds of incurring an economic cost, although was associated with a \$1.49 lower amount spent controlling for covariates. While a 14% to 11% reduction in diarrhea prevalence was observed, it is difficult to infer causality due to study design limitations. Estimates of cost-effectiveness were highly dependent on covariates included, never falling below 95% certainty in the fully specified and interacted model. The cost-effectiveness of the program bundled with other services was favorable relative to a ceiling ratio of per capita Gross National Income.

Conclusions: The DAZT intervention was cost saving to caregivers and may be a good investment in rural Gujarat based on its potential impact on diarrhea outcomes. With investment decisions based on expected values of the data taken at face value, the program is recommended in terms of cost-effectiveness. Zinc and oral rehydration salts may be bundled with other services, while maintaining cost-effectiveness.

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AIC	Akaike's Information Criterion
ANC	Antenatal care
ANM	Auxiliary Nurse Midwife
ARI	Acute Respiratory Infection
ART	Antiretroviral Therapy
ASHA	Accredited Social Health Activist
AWW	Anganwadi Worker
BIBCOL	Bharat Immunologicals and Biologicals Corporation Limited
BMGF	Bill and Melinda Gates Foundation
BIC	Bayesian Information Criterion
BPL	Below Poverty Line card
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHERG	Child Health Epidemiology Reference Group
CHWs	Community Health Workers
CMH	Commission on Macroeconomics and Health
CUA	Cost-Utility Analysis
DALYs	Disability Adjusted Life Years
DAZT	Diarrhea Alleviation through Zinc and ORS Therapy program
DCP2	Disease Control Priorities Project Second Edition
DPT	Diphtheria Pertussis Tetanus
DSS	Demographic Surveillance System

EPI	Expanded Program on Immunization ,
EVPI	Expected Value of Perfect Information
FHI-360	Family Health International 360
GAPPD	Global Action Plan for Pneumonia and Diarrhea
GBD	Global Burden of Disease study
gCEA	Generalized Cost-Effectiveness Analysis
GDP	Gross Domestic Product
GEMS	Global Enteric Multicenter Study
GLM	Generalized Linear Model
GNI	Gross National Income
GOBI-FFF	Growth monitoring, Oral Rehydration Salts, Breastfeeding , Immunization, Family Spacing, Food Supplements, and Female education
HiB	Haemophilus Influenzae type B
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICDDR,B	International Center for Diarrheal Disease Research, Bangladesh
ICER	Incremental Cost-Effectiveness Ratio
IMF	International Monetary Fund
IMNCI	Integrated Management of Neonatal and Child Illness
IQR	Inter-Quartile Range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LiST	Lives Saved Tool
LHV	Lady Health Visitor
LMICs	Low and Middle Income Countries
MHFW	Ministry of Health and Family Welfare

MICS	Multi-Indicator Cluster Survey
MMPHW	Male Multipurpose Health Worker
MO	Medical Officer
MSH	Management Sciences for Health
NFHS	National Family Health Survey
NGO	Non-Governmental Organization
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRHM	National Rural Health Mission
ORS	Oral Rehydration Salts
ORT	Oral Rehydration Therapy
PHC	Primary Health Center
POUZN	Point of Use water disinfection and Zinc treatment
PPP	Purchasing Power Parity
RCT	Randomized Controlled Trial
RDT	Rapid Diagnostic Tests
RSBY	Rashtriya Swasthya Bima Yojna
SHOPS	Strengthening Health Outcomes through the Private Sector
SMS	Short Messaging Service
SNL	Saving Newborn Lives
SUZY	Scaling Up Zinc for Young children
UK	United Kingdom
UNICEF	United Nations Children's Fund
UP	Uttar Pradesh
USA	United States of America
USAID	United States Agency for International Development

WASH	Water Sanitation and Hygiene
WDR	World Development Report
WHO	World Health Organization
WHO-CHOICE	World Health Organization CHOosing Interventions that are Cost-Effective
YLD	Years Lived with Disability
YLL	Years of Life Lost

1 Introduction and background

1.1 Problem statement

Worldwide, diarrhea is fourth only to pneumonia (17%), complications of preterm birth (15%), and complications during birth (10%) as the leading cause of mortality among children under 5 years old, accounting for 9% of total deaths (1), and killing more children than HIV, malaria, and measles combined (2). Annual mortality from child diarrhea has declined from 4.6 million in 1980 to 700,000 in 2011 (Figure 1) (3-5). Disability Adjusted Life Years (DALYs) decreased by 51% since 1990 to 89 million in 2010 (6), mostly due to averted mortality (7). In low- and middle-income countries (LMICs), the incidence of diarrhea in children under 5 is 2.9 (2.3-3.4) episodes/child year (2010 estimate) (8), but only 39% of children are treated appropriately (9). These trends are occurring in the context of a triple burden of disease (10, 11), particularly in countries in economic transition (12, 13), and difficult decisions exist in balancing infectious disease programs against other priorities.

1.2 India profile

India is a lower middle income country in southeast Asia with a per capita Gross National Income (GNI) of US$1,530 (14),[1] a Gini coefficient of 33.9 (14),[2] and a rapidly increasing lifespan (15).[3] Mortality among children under five years old decreased from 109 to 74 per 1,000 between 1987-91 and 2001-5 (16). India has had success in its infectious disease agenda, such as eradicating polio,[4] and the elimination of several other diseases is predicted for the near future (17). However, infectious disease continues to account for 30% of India's disease burden, with

[1] The range used by the World Bank for defining a lower middle income country is $1,036-$4,085 (World Databank 2013)
[2] The Gini coefficient in the United States is 46.9, reflecting more inequality. In India people are more equal because so many people are poor.
[3] There was a gain in life expectancy of 21 years between 1970 and 2010
[4] http://www.unicef.org/india/health_3729.htm

diarrhea accounting for 5.7% (18). Between 1990 and 2010 diarrhea fell from first to third largest contributor of premature death to the burden of disease (19), although India is still recognized as one of 15 high burden countries that account for 53% of global episodes, with 312.22 million episodes and 205,600 deaths each year nationwide (5). Approximately 9% of children under 5 experience diarrhea in any given two week period (16).

1.3 Gujarat profile

The state of Gujarat is in the northwest corner of India, bordering Maharashtra to the south, Madhya Pradesh to the east, and Rajasthan and Pakistan to the north. It has an area of 75,685 square miles, with a 992 mile coastline bordering the Arabian Sea, most of which is on the Kathiawar peninsula.[5] The capital city is Gandhinagar, with the largest cities being Ahmedabad (5.6 million), Surat (4.5 million), and Vadodara (1.7 million).[6] 57.40% of the state is rural (20),[7] with desert in the north and northwest, wetlands in the west, forests in the east, and fertile farmland in the south.

The official languages in Gujarat are Gujarati and Hindi,[8] with the most widely spoken language being Gujarati. English is spoken by a substantial number of people, particularly in urban areas, and different regions have a wide variety of languages and dialects. The ‘tribal belt’ of north India extends to Gujarat, with forest tribes and forest dwellers in East Gujarat. Currently, it is one of the fastest developing states in modern India, although vestiges of the caste system leave many people in rural areas in poverty traps (21).

[5] http://www.britannica.com/EBchecked/topic/249059/Gujarat
[6] http://www.census2011.co.in/census/state/gujarat.html
[7] http://www.census2011.co.in/census/state/gujarat.html
[8] http://www.britannica.com/EBchecked/topic/249059/Gujarat

Industrial development in Gujarat has been substantial, with the largest oil refinery in the world (Jamnagar) (22), commissioned as a special economic zone in 2008.[9] Other important industries include textiles, machinery, metal products, chemicals and minerals, rubber and plastic, wood and paper, and food (23). Engineering output has flourished, accounting for 9% of the national total (24). Large scale agriculture has grown, particularly for cash crops such as cotton, tobacco, groundnuts, and sugar cane – in addition to grains, oilseeds, vegetables and spices (25).

The 2011 population in Gujarat was 60,439,692 (6.04 crores), ranking 10th among Indian states, and being similar in population size to the United Kingdom (UK) (20). Nationwide, Gujarat accounts for 5% of the population of India, and has shown growth in recent years (19% per year) (20). Population density is about 300 people per square mile, below the national average. 57.4% live in rural areas, although this proportion is decreasing (20). The sex ratio in rural areas of Gujarat is 949 females per male, which is approximately the natural sex ratio, and above the national average of 933 (20).

Literacy in Gujarat in 2011 was 71.7% in rural areas (86.3% urban), with a female literacy rate of 57.8% (20).[10] This amounts to 21.4 million illiterate people, although the government is making efforts to improve literacy in the state. About half of age-eligible children in marginalized groups use services offered by Anganwadi centers, such as preschool, immunization, and supplementary food (20). The infant mortality rate was 58 in rural areas, which is approximately the national average. 45% of children age 12-23 months are fully vaccinated against the six major childhood illnesses (tuberculosis, diphtheria, pertussis, tetanus, polio, and measles), and 5% received no vaccination at all (26). 13% of children in rural areas had diarrhea in the two weeks prior to the survey, with 52% taken to a health facility (26). 25% received Oral Rehydration Salt (ORS)

[9] A Special Economic Zone is an area with different business laws to the country in which it is located
[10] http://www.census2011.co.in/census/state/gujarat.html

packets, 9% received antibiotics, 27% received another drug, and 36% received no treatment (26). 3.5% of children in rural areas had symptoms of Acute Respiratory Infection (ARI) in the previous two weeks, and 13.8% had a fever (26). 51.5% with symptoms of ARI were taken for treatment from a health facility or provider, and 3% received antibiotics (26).

1.4 Types of diarrhea and its persistence in India

Diarrhea is mainly caused by fecal-oral transmission of viruses, bacteria, protozoa, and helminthes (4). Rotavirus is the most common cause of diarrhea, accounting for 40% of hospital admissions, 100 million episodes of acute diarrhea each year (9), and is the leading cause of diarrhea death (27). *Escherichia coli*, *Salmonella*, *Shigella*, *Campylobacter*, and *Vibrio cholerae* are other main causes of diarrhea, with *Shigella* and amoebas the most common causes of dysentery.[11]

Three types of diarrhea syndromes exist including acute watery diarrhea, persistent diarrhea, and bloody diarrhea. Acute watery diarrhea results in dehydration with 250 mg/kg stool losses per day and usually lasts for several hours. It has multiple etiologies (usually rotavirus, enterotoxogenic *Escherichia coli*, or *Vibrio cholerae*) and is most dangerous in young infants (4, 9). Persistent diarrhea lasts 14 days or longer, is associated with malnutrition either preceding or resulting from the infection, and can lead to wasting. Bloody diarrhea indicates intestinal damage caused by inflammation, is most commonly caused by *Shigella*, and occurs more often in an episode of persistent rather than watery diarrhea (2). Dysentery is a specific form of bloody diarrhea consisting of the passage of frequent small volume, bloody mucoid stools, abdominal cramps, and tenesemus (a severe pain that results from trying to pass a stool) (4).

[11] http://www.who.int/topics/dysentery/en/

Diarrhea kills children principally through loss of water and electrolytes.[12] Children are particularly at risk as a greater proportion of their body weight is water compared to adults. If they survive, long term sequelae may include impaired physical growth, cognition, and concentration (4). In addition, obesity and related conditions can occur later in life such as cardiovascular disease and diabetes (28).

A combination of economics, culture, and health systems factors have led to the persistence of diarrhea in India. India accounts for nearly two thirds of the 1 billion people worldwide that practice open defecation (29). Poverty is widespread with lack of improved sanitary facilities affecting 792 million people (29), in addition to inadequate housing, crowded living conditions, dirt floors, inadequate access to sufficient clean water, cohabitation with domestic animals, and a lack of refrigerated storage of food (4). Historically, there has been a lack of adequate medical care that people can afford and access, although close to client services are being improved through the Accredited Social Health Activist (ASHA) program. The ASHA program was started in 2005, and has since scaled up to having 835,808 ASHAs in 2011, which is 94% of its target of 1 ASHA per 1000 people (30). To different extents, other risk factors may be amenable to change. For example, Bangladesh reduced the percent of people practicing open defecation from 34% to 3% between 1990 and 2012 (29), although the feasibility of achieving this level in Gujarat will be affected by the growth of infrastructure and social and cultural factors. For example, Gujarat is 89% Hindu, where Bangladesh is 90% Muslim,[13] and open defecation is 40% more prevalent among Hindus despite being more educated and wealthier than Muslims in India (31).[14]

[12] http://www.who.int/mediacentre/factsheets/fs330/en/

[13] http://censusindia.gov.in/Census_Data_2001/Census_data_finder/C_Series/Population_by_religious_communities.htm
https://www.cia.gov/library/publications/the-world-factbook/fields/2122.html

[14] A key determinant of diarrhea transmission is the defecation practices of a person's neighbors and people often live near other people of the same religion in India.

The poverty headcount ratio of people living below \$1.25 per day in India was halved between 1978 and 2010 to be 32.7% (14), and Gini coefficient has increased to 23.8 in rural Gujarat (32).

1.5 Intervention and barriers

Oral Rehydration Salts (ORS), recognized as potentially one of the most important medical advances of the 20th century (9, 33), is the standard treatment for diarrhea to replace lost fluids and electrolytes. ORS consists of sodium, chloride, potassium bicarbonate, citrate and glucose or another form of sugar and starch mixed with water to form an electrolyte solution (34). After its scientific development in Dhaka and Calcutta in the late 1960s (35), the use of ORS spread rapidly, reaching coverage levels of 25% and access levels of 60% worldwide by the mid-1980s and achieving high levels of local production with two thirds made in LMICs (36). In 2004, the 311 mmol/L formula was replaced by a 245 mmol/L formula as it was associated with less vomiting, stool output, and need for unscheduled intravenous therapy (34), as well as being 17% less expensive than standard ORS (37). In India, ORS costs only \$0.20-\$0.35 for a 20g sachet (38), and national estimates of the proportion of children with diarrhea that receive ORS has risen dramatically from 26% in 2005-6 to 43% in 2010 (39, 40).

In 2004, the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) advocated that zinc supplementation be used with ORS for managing diarrhea among young children, both to treat existing disease and avert further episodes (41). In 2006, the Government of India incorporated this recommendation into its national policy, making zinc and low osmolarity ORS part of its Integrated Management of Neonatal and Childhood Illness (IMNCI) strategy (42). The dose of zinc recommended was 20 mg per day for 10-14 days (10mg per day for infants under six months) (41). This recommendation cites a pooled analysis of ten trials that found that zinc has beneficial effects on both incidence and prevalence (43).[15] Subsequent to zinc supplementation becoming the recommended treatment, nine meta-analyses confirmed its overall effectiveness in reducing duration and severity of diarrhea (44-52), although there is a significant amount of heterogeneity among patient subgroups (49, 51). Lazzerini et al (2013) (51) present results indicating that child age and nutritional status are important, particularly in zinc deficient children. In addition, effect size varies in different Asian studies. Four studies were reviewed from the community setting evaluating zinc supplements (53-55).

The public health and policy importance of zinc research in India is enormous. With a drug cost of $0.28-$0.75 for 10-14 days treatment of ORS and zinc (56),[16] appropriately treating all child diarrhea episodes in India costs $92-$246 million (5). However only 54% of caregivers that receive a prescription adhere to the full dose in rural areas (57), and only 0.2%-0.3% of children with diarrhea receive zinc (16). Policy reasons include that zinc was only added to the National List of Essential Medicines India in 2011 (58), and that the formula included syrup, not the dispersible tablets advocated by the Government and used in the National Rural Health Mission (NRHM) (59, 60). There is ambiguity of the official policy of the Drugs Controller General of India around whether zinc is a prescription drug (56). In addition, the Drug and Remedies Act regulations impose restrictions on the stocking and sale of zinc, preventing end users from obtaining ORS and zinc from a single supplier (61).

Economic barriers present further problems. Supply-side barriers include the low profit margin given the official wholesale price and input prices (staff, capital equipment, buildings), lack of

[15] Zinc is thought to avert diarrhea morbidity and mortality by strengthening the immune system, improving absorption of water and electrolytes in the intestines, enhancing the regeneration of the gut epithelium, increasing levels of enzymes in the epithelium, and helping the body clear diarrheal pathogens from the intestines (Baqui et al 2002).

[16] Calculated from costs of INR 13.68 for 100 zinc tablets, and INR 1.58 per sachet of ORS, and 1 INR = 0.0160485 USD (www.xe.com 19 Nov 2013). $0.75 derives from drug costs from the International Drug Price Indicator Guide.

knowledge of technology and treatments among manufacturers, and low levels of management efficiency (62). Prescribers are reluctant to prescribe zinc (56), and when they do, usually prescribe syrup form (61). It is not clear if zinc is included in supply kits provided to ASHAs (61). In addition, locally produced zinc may be of questionable quality, and there is no current global funding mechanism for financing zinc through international support (37). Demand-side barriers include lack of knowledge among caregivers about zinc, reluctance to give treatment after diarrhea is over, palatability issues, and need for a prescription (56).

Community based programs have been developed as potential solutions for scaling up zinc for treatment of child diarrhea, such as the Anganwadi worker (AWW) program evaluated in the Haryana India trial (63). These workers are particularly essential to address shortfalls of higher cadre human resources in rural areas of India (64), which are served by 40% of India's health workforce (65) but are home to 68% of the population (14).

The private sector is particularly important for addressing barriers to diarrhea treatment in India. As mentioned above, it has been effectively utilized in previous research on delivering zinc at the community level in Haryana India (63). In formative research for the DAZT program, 73% of caregivers in Gujarat sought treatment for diarrhea from private providers (66). However, if current health systems trends continue, health care costs are expected to rise and inequalities in access are expected to widen (67). More research is needed on feasible delivery mechanisms of zinc that balances public and private sector channels.

Zinc supplementation may have a favorable impact on health systems costs. Patel et al (2003) found that adding zinc and copper to ORS treatment decreased costs of diarrhea treatment by 8% in hospitalized children (68). At public hospitals in India, the government pays two thirds of the cost of diarrhea treatment (69), and the potential cost savings are substantial. In the second half of a trial in Haryana India which delivered zinc through both facility and community based workers, user costs for diarrhea treatment declined by 70% in the intervention arm and 46% in the control arm (70). In 2005 in Pakistan, a training, provision, and marketing program was implemented through facility and community channels of both the public and private components of the health system (71). This program lowered household costs by 12.8% ($0.50), but increased the cost to the health system overall (71). In 2006 in Mali, zinc and ORS were introduced at first level facilities which passed drug kits to community health workers. This program increased ORS use rates by 10% to 43%, doubling sales levels in the community (72). Households incurred a mean total cost of between $0.17-$0.19 per case, and CHWs sold $5.81 worth of ORS in the intervention area and $2.80 in the control area over the course of the trial (72). Cost savings are possible due to reductions in prescriptions of antibiotics, which are prescribed to 80% of patients in India whether they are needed or not as providers are overly cautious about not neglecting to treat a relevant infection (38). In addition, demand for antibiotics among caregivers is high, as they are perceived as the strongest and most effective treatment for this deadly disease (73).

1.6 Diarrhea Alleviation through Zinc and ORS Therapy (DAZT) program

From 2010 to 2013, the Diarrhea Alleviation through Zinc and ORS Therapy (DAZT) program was conducted in 12 districts of Uttar Pradesh and 6 districts of Gujarat, supported by the Bill and Melinda Gates Foundation (BMGF) (38, 74).[17] These states were chosen as they have particularly low levels of diarrhea treatment (any Oral Rehydration Therapy (ORT) or increased fluids) at 29% in Uttar Pradesh and 63% in Gujarat (39). The DAZT program had a 'before and after' study design, with an initial survey conducted in Mar-June 2011 representing the 'before' phase, phase 1 occurring between May 2011-Oct 2011, and phase 2 occurring from Nov 2012-Dec 2013. It

[17] Districts in Gujarat included Banas Kantha, Sabar Kantha, Patan, Surendranagar, Dohad, and Panch Mahals. Districts in Uttar Pradesh included Kanpur Dehat, Lucknow, Sitapur, Hardoi, Faizabad, Sultanpur, Budaun, Shahjahanpur, Barabanki, Unnao, Bareilly, and Ambedkar Nagar (FHI-360, 2013).

was a follow on to the Point of Use water disinfection and Zinc treatment (POUZN) project, which made zinc available through private sector providers nationwide between 2005-10 (75). DAZT builds on POUZN by introducing zinc through all levels of the public sector and clinics in the private sector.

Interventions were delivered through two international non-governmental organizations (NGO) – FHI-360 in the private sector (74) and Micronutrient Initiative in the public sector (76) – with political and managerial support from UNICEF (Table 1). State level policy changes and agreements with professional associations, NGOs, and pharmaceutical companies provided high level frameworks to facilitate provision. Staff were trained at all levels in diarrhea epidemiology, the importance of zinc and ORS, dosing and regulatory guidelines, promotional strategies, the role of the implementing agencies, and the use of Short Message Service (SMS) messaging to monitor sales. Procurement, supply, and distribution systems were developed in both public and private sectors. At formal provider facilities in the private sector, DAZT corners were set up to create awareness among caregivers, remind providers to prescribe zinc, and track prescribing and purchasing patterns. Both sectors involved informal providers to improve coverage in patients' homes (74). Constraints to the program were weak program monitoring, difficulties in increasing the priority placed on ORS, the fact that zinc does not stop diarrhea, problems in sustaining demand, and difficulties improving standards of care and accountability of providers (38).

1.7 Other diarrhea programs delivered at scale

In addition to the POUZN and DAZT programs, there are a number of at-scale private sector projects emerging in the implementation science literature. These evaluations consist mainly of project reports, with a few published studies. The Scaling Up Zinc for Young children (SUZY) project in Bangladesh represents one of the first national scale zinc programs, occurring between 2003-8 and rolling out zinc in 2006 (77-79). The Strengthening Health Outcomes through the

Private Sector (SHOPS) program is the United States Agency for International Development's (USAID) principal initiative to strengthen the private sector to provide services addressing a wide variety of priority disease areas including zinc for diarrhea. Since its inception, SHOPS has expanded to fourteen countries in Africa (Benin, Ghana, Kenya, Madagascar, Malawi, Mali, Nigeria, Tanzania, and Uganda have zinc programs), four countries in Asia and the Middle East (India, Bangladesh, Jordan, and Nepal have zinc programs), four countries in Latin America, and Russia in Eastern Europe (80).

The SUZY program in Bangladesh was led by Charles Larson of the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B) in collaboration with the Ministry of Health and Family Welfare (MHFW) and Acme Laboratories (79). SUZY focused primarily on the private sector based on results from formative research, which indicated that it was the source of care for 90% of caregivers that sought attention (77). Initial research also developed key messages for marketing,[18] and determined that most poor people in rural areas would be willing to pay $0.25 for a 10 tablet blister pack (77). Safety was established through a series of randomized control trials, one in Bangladesh, in addition to monitoring outcomes among 24,000 patients at the ICDDR,B hospital (77). The patent for the dispersible zinc pill was obtained from the French company Nutriset and approval was obtained from the Bangladesh Drug Administration for Acme Laboratories to produce and distribute a 20mg product branded BabyZinc (79). The MHFW created two governmental committees in support of the zinc scale up, and the Bill and Melinda Gates Foundation contributed $8 million in funding through the course of the project (79).

[18] The four key messages that the SUZY program targeted towards caretakers included 1) Baby Zinc is for the treatment and prevention of diarrhea 2) One tablet should be taken each day for 10 days 3) Dissolve the tablet in water 4) Use in conjunction with ORS

The outcomes of the program were that there was a rapid increase in awareness about zinc among caregivers, followed by an increase in its use (10% in rural areas, and 26% in city non-slum areas), and no decrease in coverage of ORS (77). The poorest households spent an average of $0.50 per episode, and the average amount households were willing to pay for a ten day course of zinc after explanation of benefits was $0.45 (77). Mainly through information from the pharmaceutical industry, caretaker awareness of zinc increased from 5% to 50% in rural areas, and 90% in urban non-slum areas (78).

1.8 Bundling services

Bundling services into packages that can be delivered by one modality of the health system has been discussed as a policy strategy for improving efficiency. Early thinking about bundling services was stimulated by the essential health packages designed by the World Bank and WHO in the 1990s (81), and the Commission on Macroeconomics and Health (CMH) report (82). In addition to efficiency, poverty reduction and equity have been highlighted as benefits as many of the interventions included address illnesses that affect the poor (81). However, services are often 'Bundled out of logistical convenience, donor directives, organizational expertise, or specific lines of scientific inquiry rather than consideration of delivery mode, biological or behavioral synergy, or cost effectiveness' (83). Further work should evaluate the cost-effectiveness of different packages of services for preventing and treating major causes of child mortality.

2 Thesis overview

2.1 Study aims

The aims of this study are to describe the factors influencing odds of having a cost of diarrhea treatment, amount of cost, and cost-effectiveness of the DAZT program in Gujarat India. It advances the current body of knowledge by using a multistage modeling approach assessing the importance of the health systems intervention, use of zinc and ORS, source of care, wealth quintile, and other factors.

Aim 1: To estimate the odds that caregivers of children with diarrhea incurred an economic cost during the child's last episode of diarrhea, estimate the magnitude of economic costs, and evaluate which factors influence these outcomes.

- This aim was evaluated with a two-part model, using a multivariable logistic regression followed by generalized linear modeling with a gamma distribution. The hypothesis of the first part is that the proportion of children incurring a cost will remain equivalent after the introduction of the program as compared to before, if not increase since more children are expected to receive treatment. It is expected that costs were incurred more frequently for younger children and those of mid-range wealth index quintiles (84). Hypotheses for the second part are mixed whether magnitude of costs will increase or decrease after program implementation. In favor of an increase, zinc supplements add an additional cost and the amount of ORS consumed may increase (37, 85). In favor of decrease, inefficient drug prescription patterns are likely to be reduced, cases may become less severe, and fewer hospitalizations may be necessary. Costs are expected to have an upside down U-shaped curve with the least and most wealthy quintiles having the lowest costs (84). Older children are expected to incur lower costs due to their stronger health status relative to children under six months (85). Caregivers seeking care from government facilities are expected to have lower costs.[19]

Aim 2: To estimate the cost-effectiveness of zinc provision through the DAZT program relative to the status quo that preceded the program adjusted for covariates.

- This aim will be evaluated using a multivariable linear regression framework, using a methodology that combines economic evaluation and econometric methods described by Hoch et al (2002) (86). The hypothesis of this aim is that the program was cost-effective relative to status quo conditions at the start of the survey due to improved health outcomes and economic cost saving to caregivers. It is not expected that the intervention was more costly with more health benefit, consistent with other studies (68, 87), since program costs are expected to be substantial in the intervention phase (70). However, results are expected to remain highly cost-effective.

Aim 3: To calculate the modeled cost-effectiveness of delivering zinc as a bundled package of interventions to prevent and treat diarrhea and pneumonia

- This aim builds on methods from previous work for calculating the cost and cost-effectiveness of bundled services (88-90). The hypothesis of this aim is that cost effectiveness of bundling services is synergistic, with the bundled services being more cost-effective than the services provided individually (89), since several interventions can be delivered through the same modality.

[19] Only nominal user fees of Rs 5 (US$0.12) were charged for outpatient visits at government run health facilities in 2007 in Uttar Pradesh (Rao and Peters 2007) and the public sector also levies nominal charges in Gujarat (Krishna Rao, personal communication).

2.2 Rationale

2.2.1 General project rationale

Results from this project will inform policy making related to child health in low- and middle-income countries (LMICs). Across countries, only modest progress has been made in increasing coverage of ORS in LMICs (91), and coverage of zinc is surprisingly low. Evidence is needed to make zinc supplementation an international priority and scale up its use for children with diarrhea (37). The Dissertations Abstracts Database indicates that while doctoral research on tuberculosis and malaria has steadily increased in recent decades, the number of dissertations on diarrhea have remained relatively constant since the 1990s (92). In addition, the number of publications on diarrhea in LMICs have declined substantially since their peak in the 1990s (92).

Implementation science research on zinc in India has been conducted through the POUZN study, which indicates that diarrhea treatment can be enhanced through zinc introduction in the private sector (38, 75). However, programmatic effectiveness varies according to delivery strategy and coverage levels, and each community and geographic area presents different constraints. These factors affect impact, and little is known about the cost and cost-effectiveness of different approaches delivered at scale. The analyses in this thesis can inform which program characteristics were the most responsible for achieving health systems goals and for what groups they can be achieved.

2.2.2 Costing component rationale

Despite the low cost associated with diarrhea treatment, understanding relevant determinants of costs is important. The number of people living on less than $1.25 per day in India is the highest in the world (93), making even minor costs significant barriers to health care. In addition, episodes occur frequently among children in LMICs (1.7-3.5 episodes per child per year) (4, 59). Understanding costs can help policy makers understand the impact of treatment and the disease burden on the economic well-being of households, inform financing schemes to enhance risk pooling, promote equity, and promote a positive perception of the health system. From a programmatic perspective, costing data is helpful to inform plans for scaling up interventions.[20] Studies exist to evaluate the cost of zinc supplementation for hospitalized cases of diarrhea (68, 85) as well as studies that use population level survey drawn from the Demographic Surveillance System (DSS) (94, 95), and community based surveys (70, 96). Only two studies evaluate factors associated with costs (85, 95), and neither is from a program setting. From an implementation science perspective, evaluating the incremental cost of delivery strategies of health interventions is a key research priority (97).

2.2.3 Cost-effectiveness component rationale

Evidence to promote diarrhea management programs and improve efficiency in the health sector is particularly important in India where a LMIC level budget is spread thinly across a massive population (14, 98). Cost-effectiveness analysis (CEA) is a useful tool for informing prioritization decisions between unrelated health care interventions to maximize health gain given these limited health budgets. Currently, PubMed reveals over 30 English language cost-effectiveness analyses evaluating interventions in the Indian context; however the set of interventions relevant to India's health sector that has been assessed is far from complete. A growing body of knowledge supports the effectiveness and cost-effectiveness of zinc supplementation in hospital settings and economic modeling studies (4, 68, 87, 99); and further cost-effectiveness work was ranked as a research priority using the Child Health and Nutrition Research Initiative framework (100) (although the cost-effectiveness of zinc was not mentioned in a similar study in 2009 (101)). In particular, evidence for its cost-effectiveness in real world conditions must be strengthened.

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[20] Costs to caregivers can be used to predict demand for services, and might be considered when devising revenue generating strategies to finance scaling up of this type of program.

Methodologically, cost-effectiveness analyses of before and after studies are emerging (102-107); however, these studies are not well established in the literature and thought is needed about methodological considerations that should be made for evaluating these studies. For example, before and after studies often overstate treatment effect and may require adjustment. The Cochrane Consortium provides some guidance for other sources of bias (108), however, specific methods for evaluating these studies need further development.

The net benefit regression approach is relevant for this type of analysis two main reasons. First, when covariates are important for equity considerations, this technique can have relevant policy implications (109). For example, it can address the question of how cost-effective it is to provide the intervention to people according to wealth quintile. Second, net benefit regression is relevant to control for confounding. While the approach is equally valid for randomized (86, 110) and non-randomized studies (109, 111), it may be even more appropriate for non-randomized studies as covariates are even more likely to be unevenly distributed across study phases than in RCTs (112). Kreif et al (2013) note that most cost-effectiveness analyses of studies with a non-randomized design do not account for imbalances in covariates, which can lead to biased estimates of cost-effectiveness (113).

2.2.4 Cost-effectiveness of bundled services rationale

Model results are mixed whether bundling services enhances the cost-effectiveness of their delivery. A study by Darmstadt et al (2005) suggests that newborn health services become more cost-effective when delivered in packages, although the risk of over-bundling is noted (89). World Health Organization Choosing Interventions that are Cost-Effective (WHO-CHOICE) models show that cost-effectiveness became less favorable with additional services added to delivery packages of child health interventions (102). An existing projection of the costs and effects of scaling up interventions to prevent and treat diarrhea relies on old data (90), which overestimates worldwide levels of child mortality due to diarrhea (5, 114). Other precedent exists in several studies that evaluate the costs associated with interventions associated with the Lives Saved Tool (LiST), which use a variety of primary and secondary data sources to calculate costs (90, 115-118). Further data exists from the Haryana India trial (70), estimates can be refined through consultation with local stakeholders, and full cost-effectiveness analysis is needed.

2.3 Organization of the document

This dissertation follows a progression from a review of previous work, describing elements of cost-effectiveness analysis, presentation of the three analyses conducted, and finishing with a discussion of their relevance to policy. Chapter 3 reviews costing and cost-effectiveness studies from India and similar countries, including a review of studies that use a net-benefit regression framework in the LMIC context. Chapter 4 discusses key concepts in health economics and economic evaluation, philosophical underpinnings of economic evaluation, and a continuum of research through which evidence can be built up to inform policy. It concludes by connecting a conceptual framework based the Andersen and Newman framework for treatment seeking to the study questions of this thesis (119). Chapter 5 discusses key topics relevant to understanding the methods used in data collection and the analytic approaches taken. Chapter 6 (paper 1) evaluates the impact that the DAZT program had on economic costs to caregivers of infants with diarrhea, and shows which covariates were associated with the count and amount of these costs. Chapter 7 (paper 2) evaluates the cost-effectiveness of the DAZT program using net-benefit regression methods to control for imbalances in covariates resulting from its study design (86). Chapter 8 (paper 3) evaluates the cost-effectiveness of zinc and ORS in the broader context of the set of preventive and curative interventions that can be used to address the burden of diarrhea and pneumonia through the health sector, quantifying lives saved with LiST tool projections and uncertainty around estimates using probabilistic sensitivity analysis. Chapter 9 summarizes findings and discusses key topics that flow from them that are relevant to policy. It indicates the strengths and limitations of this research, identifies areas of further study, and provides conclusions of the overall dissertation.

3. Literature review

The purpose of this literature review is to describe the evidence base that puts results from this dissertation research into context, and to provide ideas for analytic methods. Described studies include evaluations of similar programs providing zinc at scale, evaluations of expenditures associated with diarrhea treatment according to covariates, cost-effectiveness analyses of the therapeutic use of zinc to treat child diarrhea, cost-effectiveness analyses that have been done in LMICs according to the net-benefit regression approach developed by Hoch and colleagues (86), reviews that summarize subgroup analyses on zinc supplementation for child diarrhea, and economic evaluations of bundled services.

3.1 Costing studies

Patel et al (2013) evaluated the importance of different factors on cost of diarrhea treatment in a hospital setting through a linear regression framework in Nagpur India (85). The average cost of treating a diarrhea episode without zinc was $15.19 (sd $7.18). Cost of treatment was more in the supplemented group due to the cost of the zinc supplements and the fact that more ORS was consumed. Other determinants of total cost included older ages, hospital days, intravenous fluid use, dehydration, use of antibiotics, and complications. A methodological limitation of Patel et al (2013) was that it did not retransform variables onto their original scale with a smearing estimator (120). In addition, its single hospital perspective is of limited application to health systems planners interested in a broader perspective on the economic impact of widespread introduction of zinc into a geographic area.

Rheingans et al (2012) evaluated the cost of diarrhea treatment in Bangladesh, India, and Pakistan as part of the Global Enteric Multicenter Study (GEMS) (95), with the study site in India located in Kolkata, West Bengal (94). Average costs per episode in India were $3.33, mainly due to direct medical costs. As expected, costs had a positive skew, with 10% of episodes having a cost exceeding \$8.07. Logistic regression was performed on the log odds of incurring costs; however, other forms of regression were not conducted due to small sample size (n = 154). Direct and total medical costs were stratified by wealth quintile (classified by principal components analysis), sex of child, maternal education, age of child, severity of episode, and duration of episode. Of note, poorer households had lower direct and total costs, possibly indicating that they were not adequately accessing the health system; however, this result was only marginally significant. In addition, richer families had lower costs, producing an upside-down U-shaped curve. Older children incurred lower costs due to the greater effectiveness of zinc in that cohort (51). 87% of costs were in the formal sector, possibly reflecting the use of ORS and other low cost interventions from chemists. 48% of out of pocket expenditures were from savings. There was little difference between costs among girls and boys.

A second study was published with results from the African countries of the GEMS trial, including Gambia, Kenya and Mali (84). The range of total costs was narrower than in Asia, ranging from \$2.63-\$6.24, with the data having the expected positive skew. Expenditures for each episode according to the socioeconomic status of the household had a U-shaped curve in Gambia, was relatively uniform in Kenya, and had an upside-down U-shaped curve in Mali. Like India, there was not a significant difference in expenditure between boys and girls, women with different levels of education, children of different ages, and different severity of diarrhea.

As Patel et al (2013) transformed costs in their model (85), neither two-part models nor gamma regression have been used to evaluate costs associated with child diarrhea treatment in LMICs. However, the probability of treatment seeking and out of pocket costs among the elderly in China has been modeled with a two part model using gamma regression (121). A study from Finland compared the performance of an unadjusted bootstrap approach to cost-effectiveness analysis to a two-part modeling approach using logit and gamma regressions (122). This study emphasized the importance of controlling for covariates when evaluating an observational study.

3.2 Cost-effectiveness analyses

Cost-effectiveness analyses evaluating zinc and ORS for treating child diarrhea have found mixed results between evidence in favor (68, 87, 99, 102), and more recent evidence against which emphasizes the importance of heterogeneity and context (85). Study designs have included randomized controlled trials (68, 70, 85, 87) and secondary data analyses (4, 99). Other evaluations have been done on widespread prophylactic zinc supplementation to prevent diarrhea (102, 123-125), and cost-benefit analyses were performed as part of the Copenhagen Consensus on disseminating iron and zinc dense rice (126), prophylactic zinc supplementation for children 6-12 months as part of a set of micronutrients (127), and zinc supplementation alone for children 6-59 months (128). However, this review will focus on CEA of therapeutic zinc supplementation of ORS to treat acute diarrhea.

3.2.1 Trial based evaluations

Patel et al (2003) evaluated the cost-effectiveness of zinc and copper supplements and standard ORS compared to standard ORS alone for treating 200 children 6-59 months old with acute diarrhea at a government hospital in Nagpur India (68). This study took a patient's and provider's perspective to costing, and evaluated outcomes as deaths averted and cases averted. The intervention was found to cost $14 per child and have dominant cost-effectiveness, although confidence intervals of both costs and effects included zero (dominance was not statistically significant). As Lefevre points out (129), the generalizability may be limited as the dose of zinc was two times the WHO guidelines (40 mg instead of 20mg) (41) and copper was also administered with the zinc. In addition (129), standard ORS was used instead of the reduced osmolarity formula (44), although the latter can be expected to improve cost-effectiveness as it is more effective (41) and 17% cheaper than standard ORS (37). Finally, the duration of supplementation was not mentioned and a non-standard discount rate of 5% for LMICs was used (88, 130).[21]

Gregorio et al (2007) evaluated the cost-effectiveness of zinc supplementation to ORS relative to ORS alone among 117 patients presenting to the emergency room of a government hospital in the Philippines (87). The WHO standard dosage of zinc (20mg for 14 days) was used in this study, although was not accompanied by low osmolarity ORS. Costing was done from a societal perspective, and outcomes were measured as day of diarrhea and case averted among diarrhea <4 days. The intervention was found to be dominant, saving $2.40 per day of diarrhea averted, although differences in costs and cost-effectiveness were not significant. There were limitations in the costing performed in this study, with utilities and building services and salary subsidies for government employees not included. In addition, direct non-medical and indirect costs were modeled instead of being based on collected data.

Patel et al (2013) evaluated the cost-effectiveness of zinc supplementation relative to two comparators, 1) zinc with copper supplementation and 2) a placebo at a public tertiary hospital in Nagpur (85). Zinc doses were set according to weight at 2/mg/kg/day for two weeks, and it is probable that low osmolarity ORS was used. Costing was conducted from a provider's perspective and patient's perspective, and outcomes were assessed per hour of diarrhea averted. Both intervention arms had higher costs with no additional benefits, contradicting the main conclusions of previous studies (68, 87, 99). Reasons for not finding a clinically significant effect are cited (131), and a sensitivity analysis from Gregorio et al (2007) is cited as corroborative evidence (87); however, reasons for having different results from their previous study are not stated (68).

[21] Drummond et al (2005) indicate that a 5% discount rate proliferated in studies published in the New England Journal of Medicine in the late 1970s and early 1980s, but that there is no rationale to justify this level.

Lefevre et al (forthcoming) evaluated the cost-effectiveness of zinc supplementation of ORS relative to standard treatment through a combination of four delivery channels in Haryana India (70). Fourteen 20mg zinc tablets and two ORS packets were administered to all children with diarrhea aged 1 month to 4 years (63). These channels included public primary health centers, public subcenters in their catchments areas, private practitioners, and home treatments by Anganwadi Workers (AWW). This study included an extensive costing exercise involving reviews of program records, in depth interviews and observation to assess staff time invested in the project, and household surveys to assess out of pocket costs. Outcomes were assessed with surveys at two points, and translated to per death and DALY averted based on assumptions about duration and mortality. Cost-effectiveness was found to be $0.24/DALY averted from a societal perspective, $13.51/DALY averted from a program perspective, and $6.68/death averted. Limitations include that costing was done on reported estimates, uncertainty was quantified on only a subset of model inputs, and results may not represent cost-effectiveness when the intervention is introduced at scale.

Most recently, an economic evaluation was conducted of scaling up zinc and ORS coverage through a social franchising program in Burma to provide a package of these interventions called Orasel in rural areas (132). This program utilized a network of private providers managed by Population Services International, providing them with regular stocks of ORS and zinc kits and training in how to distribute them. Evaluation included an extensive costing, which included packaging, marketing, and distributing zinc; while outcomes were measured in terms of deaths and DALYs averted,[22] calculated from coverage based projections estimated by the LiST tool. The wholesale cost of Orasel kits was $0.23 after subsidy, and providers were instructed to sell

[22] DALYs were based on the Years of Life Lost (YLL) component as Years Lived with Disability (YLDs) were expected to be negligible

them at a retail price of $0.35. The cost-effectiveness of the program relative to the status quo was $5,955 (IQR: $3437-$7589) per death averted and $214 (IQR: $127-$287) per DALY averted, with confidence intervals determined through Monte Carlo Simulation. However it was necessary to model some variables including adherence, attribution of overhead costs, and number of franchising officers. The generalizability is limited due to the pre-existing presence of a social franchising network. Notably, this study is the first to model uncertainty around both program costs and costs to households. The number of episodes per child appears low compared to other estimates – 0.6 per child per year compared to 1.7-3.5 reported in the literature (4, 59).

All of these studies quantified uncertainty through probabilistic sensitivity analysis using the non-parametric bootstrap (133), with one also using Fieller's theorem (87). None were powered to detect differences in mortality (68, 70, 85, 87), and none calculated the necessary sample size required or power available in terms of cost-effectiveness outcomes (134, 135). The hospital settings of the trial based studies may have important differences from the community setting such as severity of cases and intensity of treatment measures available (68, 85, 87). In two of these studies, wages lost by the caregiver was a key driver of costs (68, 87). Three studies attempted to quantify health outcomes as DALYs (68, 70, 132), although only one had reason to report incremental cost-effectiveness ratios (ICERs) with DALYs averted as the denominator (70, 132). None of these studies attempted to capture long term health effects such as cognitive deficits, stunting, and obesity and related conditions that occur later in life (cardiovascular disease and diabetes) (4, 28).

3.2.2 Model based evaluation

The first model-based estimate of the cost-effectiveness of zinc supplementation was conducted by Robberstad et al (2004) in the Tanzanian context (99). Zinc supplementation (20mg for 14 days) of standard ORS and standard ORS alone were compared to a no-treatment comparator, consistent with generalized CEA (136). Cost-effectiveness was calculated assuming two populations of children: 1) those with non-dysenteric diarrhea, and 2) those with both dysenteric and non-dysenteric forms. Costing was done from a societal perspective, with data drawn from four dispensaries. Mortality estimates were based on a meta-analysis (137), and outcomes were translated to DALYs. Calculations were performed with a disability weight of 0.119, which compares to recently released values by the Global Burden of Disease (GBD) 2010 (mild 0.061, moderate 0.202, severe 0.281) (138). A decision tree was used with probabilistic sensitivity analysis to quantify uncertainty, although with triangular distributions (which are convenient to fit but implausible representations of the true distributional form (139)). Cost-effectiveness was found to be $40/DALY averted for zinc supplementation for non-dysenteric diarrhea ($1200/child death averted), $73/DALY averted for zinc supplementation for all diarrhea ($2100/child death averted), and $113/DALY averted for ORS alone ($3,200/child death averted). Gaps existed in their costing of case management; however, authors indicate that the cost of ORS was four times more than previously reported estimates, mainly due to differences in fatality rates assumed (140). Indirect costs and effects were not included, such as wages lost for caregivers and effects on acute respiratory infection, all-cause mortality, and stunting. Capital costs were considered, but it is not clear what components they included. It is not certain whether the four dispensaries are representative, and was not clear how generalizable costs would be across settings. Nevertheless, Scoups indicates that this paper has been cited at least 30 times and has had a significant impact on public health policy (37, 69, 85, 87, 95, 141, 142).

Based on very old evidence from South Asia (143, 144), the cost-effectiveness of ORS was reported in the Disease Control Priorities Project second edition (DCP2); however, the benefits of zinc were not formally quantified. Included studies found a median cost per child of $2.91 (range $0.02-$5.80) (4). Estimates specific to India were calculated in a follow-on report using an expanded set of sources (102, 144-146) and finding a cost per episode of $0.07-$0.50 considering

ORT costs only, or \$5.08-\$5.51 when including other costs (147). Importantly, these studies were published before the widespread use of low osmolarity ORS, which began in the early 2000s (148).

3.2.3 Cost-effectiveness using the net benefit regression framework

Two studies have calculated the cost-effectiveness of interventions in LMICs using net-benefit regression (86), both on non-randomized maternal and newborn health programs in Burkina Faso (109, 111). The first evaluated the Skilled Care Initiative, calculating cost-effectiveness according to head of household education, distance to facility, and asset ownership (111). The second evaluated a community based health insurance scheme, calculating cost-effectiveness according to education, place of residence, and asset ownership (109). These studies included institutional delivery and use of health services as their program outcomes instead of DALYs or another summary measure of population health. Results are presented as tables of coefficients and ICERs, and adjusted cost-effectiveness acceptability curves (CEACs). An important distinction between these studies and our proposed research is that neither of these studies had a cluster randomized study design; therefore, they do not use generalized estimating equations or robust standard errors.

3.3 Costing of bundled services

Several studies have evaluated the costs associated with interventions associated with the Lives Saved Tool (90, 115-118). These models draw data from a variety of sources including WHO-CHOICE (90, 115, 118), the UNICEF supply catalogue (90, 115), the OneHealth tool (118), International Drug Price Indicator Guide directly (115), Marginal Budgeting for Bottlenecks tool (117), and primary source data (116, 118). This review will focus on two studies; Fischer-Walker et al (2011) for its focus on diarrhea prevention and treatment interventions (90), and Adesina et al (2013) for its focus on bundled services (118).

Fischer-Walker et al (2010) (90) calculated the costs of scaling up diarrhea related interventions for children under 5 years old according to a five year projection of outcomes for the 68 countries included in LiST. Interventions assessed included preventive measures (vitamin A supplementation, rotavirus immunization, and breastfeeding), treatment measures (ORS and zinc, antibiotics), and water, sanitation, and hygiene (WASH) interventions (improved water source, water connection in the home, improved sanitation, hand washing, hygienic disposal of children's stools). This model assumed that all children with diarrhea received ORS and zinc, and that the proportion of children with dysentery correctly received antibiotics. Costing was done using an ingredients approach, using data from the WHO-CHOICE database, UNICEF supply catalogue, and consultation with experts. WHO protocols and expert opinion were used to estimate amounts of necessary drugs, supplies, and personnel time. Results for the ambitious scenario indicated that 1 million lives would be saved in 2015, and that scaling up would cost $49.2 billion over five years. The universal coverage scenario predicted that 1.4 million deaths would be averted, costing $84.8 billion over five years.

Adesina et al (2013) (118) evaluated a broader set of child health interventions delivered at hospitals and health centers, but did not include diarrhea treatment. The importance of this model is its emphasis on bundling services. Methodologically, it used a translog function to calculate factor shares of different cost components. Facility level data were drawn from primary sources in six African countries, supplemented with indirect and direct cost data from WHO-CHOICE, and labor, consumables, and drug costs the OneHealth Tool. Results indicated a cost of $1.21 for a basic antenatal care (ANC) visit, or $4.81 for combined personnel, drugs, and consumable cost (personnel costs accounted for the largest share). Conclusions emphasized that the bundled cost of six recommended antenatal care services was 12% less than the cost of delivering them individually.

4. Conceptual framework

4.1 Definition and purpose

A conceptual framework is ‘a diagram of proposed causal linkages among a set of concepts related to a public health problem’ (149). It ‘explains graphically or in narrative form, the main things to be studied – the key factors, concepts, or variables – and the presumed relationship between them (150)’. The development of a conceptual framework is vital for this dissertation to define a research question narrow enough for analysis, and relevant to current policy. The approach taken will be inductive, with key variables chosen according to existing literature to justify them, and arranged according to the conceptual structure of Andersen and Newman (1973) (119), with diagrammatic structure expanded from Shah (151). This section will describe the theory that is relevant for this dissertation, and outline the relationships between the variables that are relevant for the regression analysis.

4.2 Health economics and economic evaluation

Health economics is the science of making choices in the face of scarcity to promote health and prevent and treat disease. While scarcity is widely acknowledged in other sectors, it is often denied in the health sector while existing in many forms; global budgeting in the UK National Health Service (NHS), ability to pay in the USA, and systematic rationing in league table experiments such as occurred in Oregon (152). The health sector is also unique to other markets due to the extent of government involvement; uncertainty from patient, provider, and payer perspectives; imbalances of information between these parties; and significant presence of externalities (153). Analyses can have a positive or normative perspective, with positive economics describing observations about a research question, and normative economics prescribing what should be.

Prioritization of health interventions is particularly relevant in LMICs both for national health budgets and for international development assistance (154). The number of interventions available to health systems planners in the marketplace exceeds capacity to afford all of them (155), new interventions are being developed (156), and others are gaining relevance as lifespans increase and new risk factors gain importance as societies progress through the 'demographic transition' (157) and face a 'triple burden of disease' (10, 11). The population of India is increasing – currently 1.21 billion and not projected to stabilize until mid-century at 1.72 billion (12). Lifespans have increased 11 years in the last three decades to 65 (14). In addition, prioritization between interventions delivered by the health system is vital to maintain equity, which is gaining in importance as the world becomes more inter-connected, supply and human resource constraints are addressed, and people become empowered to raise their expectations and demand (156).

Despite the fact that government health expenditures are growing along with GDP (158), budgets are unlikely to be sufficient to provide universal coverage of a minimum number of services to these growing needs in the near future. In addition, current spending is very inefficient in terms of cost-effectiveness – for example, in India, open heart surgery is subsidized in national public hospitals (154), but ORS packets being used in only 26% of diarrhea episodes (16). Overseas international assistance for health is growing (159), particularly bilateral funding from the USA (160), and donors expect good return on their investment.

Development and proliferation of economic evaluation methods and published studies are making evidence based priority setting more feasible in LMICs, with at least seven Health Technology Assessment (HTA) bodies forming in upper-middle income countries (154, 161). Economic evaluation is a sub-discipline of health economics that compares the costs and health outcomes of an intervention relative to an alternative scenario to assess the extent to which it is a good investment, thus informing how to allocate limited healthcare resources. Three types of economic evaluation are available including cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA) (133).[23] CEA and CUA are identical except in their methods for assessing outcomes. CEA measures outcomes in natural units, either health outcomes or clinical objectives that can be linked to health outcomes (such as contraceptive user generated). CUA measures outcomes in terms of generic metrics that combine morbidity and mortality into a single metric.[24] The distinction between CEA and CUA is emphasized by Drummond et al (2005) (133), although the distinction was not made by the US Public Health Service (155) or WHO (162). Ratios resulting from CEA and CUA may be compared to a threshold to determine whether they are considered favorable (163), and are helpful for making decisions within specific budgets. CBA values outcomes in terms of monetary units, often in terms of willingness to pay, which is useful for allocating resources across budgets from different economic sectors. The advantage of CEA and CUA over CBA is that they make health the objective function of the health system, which is a widely accepted extra-welfarist assumption (164). CBA is grounded in economic theory, but willingness to pay may be tied to ability to pay and reflects non-health benefits of health interventions (133).

India has had mixed success in addressing challenges in the development and use of economic evaluation. Data and analytic methods for economic evaluation in low- and middle-income studies is generally of low quality, but higher quality evidence from India is proliferating through the second and third editions of the Disease Control Priorities Project and other international collaborations (147, 165-168). Local capacity to produce evidence is being further developed with the creation of an International Fellowship on Health Technology Assessment to provide

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[23] Cost minimization analysis is not included in this list as it is not considered an adequate form of economic evaluation by many economists. Relative costs between comparison strategies are not informative if it is not clear what the outcomes are of each.

[24] Such as Health Adjusted Life Years (HeaLY), Disability Adjusted Life Years (DALY), and Quality Adjusted Life Years (QALY)

training workshops.[25] However, formal institutional structures are only at their formation stage for health technology assessment (169), and it follows that legal frameworks have not yet developed either. In addition, India has had difficulty in updating benefits packages and drug lists regularly; for example, the National List of Essential Medicines of India was updated in 2011, eight years after its previous version (60), where the WHO list of essential medicines is updated every 1-3 years (170).

4.3 Philosophical underpinnings

The philosophical assumptions of this dissertation are grounded in the ethical case for supporting child health interventions. Very little direct evidence exists on the ethical motivations of zinc treatment for child diarrhea; however, reasons for protecting child health are a subject of debate in the international health community.

- Access to health care is often marginalized for children
- Children are a vulnerable population
- Zinc for child diarrhea can be a life-saving intervention
- Diarrhea affects everyone, but disproportionately affects the poor
- Diarrhea deaths are a solvable problem, despite their acceptance as inevitable by people in poverty
- Saving child lives has intergenerational effects

The case against prioritizing saving child lives exists in assumptions behind the age weighting function of the DALY formula (171). This perspective argues that young and old people depend on people between 15-50 years old for their health and survival both physically and emotionally (172). Other possible arguments are that people between 15-50 are the most economically

[25] http://healthcare.financialexpress.com/market-section/1170-fellowship-on-health-technology-assessment-hta-in-india

productive in society and that they pay the taxes that support the health system, although these considerations are rejected by the GBD team as they have undesirable implications in terms of equity.

However, the above arguments reflect a ‘human capital’ point of view, which can be countered from a variety of perspectives. Children are a vulnerable population (173), and the max-min principle of Rawls’ Theory of Justice is to improve the situation of the worst off in society (174). In addition, life-saving interventions are supported by the ‘rule of rescue’ (175), and zinc has been shown to be life-saving and effective in a variety of settings (50). However, it must be noted that the ‘rule of rescue’ refers to saving an identifiable child from imminent risk of death, when the same amount of investment could be used to protect all of the children in an entire community (173). In terms of vertical equity, diarrhea is a disease that preferentially affects the poor (4), with dysenteric diarrhea particularly affecting disadvantaged people (16), and principles of fairness give special priority to the worst off in society (176). Gujarat has levels of diarrhea treatment of 59% (39),[26] has levels of poverty around the national average (177),[27] and the poorest quintile of people in India is more than twice as likely not to receive treatment for diarrhea as those in the richest quintile (16).

This equity argument might be challenged from a utilitarian perspective according to the equity-efficiency tradeoff argument. However, equity and efficiency are not necessarily mutually exclusive; a key conclusion of the Disease Control Priorities Project is that sometimes the most cost-effective interventions are also the most equitable (178), and the CMH report indicates that sometimes investment in LMIC health sector ‘pays for itself’ in terms of economic development benefits (176). The potential for solving diarrhea deaths can be seen in the global trend (Figure 1).

[26] Including ORS or gruel, but excluding increased fluid or other home remedies
[27] The national proportion of people in poverty is 25.7%. The proportion of people in poverty in Gujarat is 21.5% and is 30.4% in Uttar Pradesh.

Child health interventions have intergenerational effects as living healthy children grow up to have living healthy children, and the objective of the DAZT program is to stimulate a virtuous cycle.

4.4 Continuum of cost-effectiveness analysis

Sculpher et al (2006) proposed an iterative approach to guide the development of economic evaluation to inform policy making (179). These stages of economic evaluation that could be relevant to the Indian HTA body (180).

1. Identify potentially relevant decision problems affecting prevention and treatment strategies affecting the Indian population. These questions could reflect priorities of the authorities of the Indian health system, international community, pharmaceutical industry, or the general public. To avoid imbalances in what research topics take priority encountered in some high income countries (181), priority setting criteria could be set according to those used by the WHO ad hoc committee (156).
    - Size of the disease burden
    - Reasons that the disease burden persisted
    - Adequacy of the current knowledge base
    - Cost-effectiveness of interventions and the probability of successful development of new tools
    - Adequacy of the current level of ongoing research and funding
2. Funding of evidence synthesis and decision modeling to address questions about whether research should be conducted or the intervention should be adopted. In India, the evidence base available for modeling for many conditions can be expected to be thin, with disproportionate amounts of research targeted towards global priority diseases. That said, WHO-CHOICE and DCP2 models could serve as starting points for making

country-specific models (as in Chow et al (2007) (147)), with parameters that lack adequate data tested in sensitivity analyses.

3. Formal research priorities should be set based on the modeling. Expected value of Perfect Information (EVPI) Analysis could be conducted to establish the key interventions to be evaluated and parameters to be researched (182, 183). EVPI is an analytical approach that is seldom used in LMIC research (184, 185), but is particularly relevant for that setting given the incomplete knowledge base for CEA modeling.
4. One or more primary studies can be conducted with pragmatic economic evaluation conducted alongside. Traditionally, this stage has focused on Randomized Controlled Trial (RCT) evidence (179); however, our study emphasizes the importance of non-randomized program evaluation to provide economic evaluation evidence using appropriate methods for controlling for confounders (86).
5. Previously developed models can be updated with evidence from the primary studies.

4.5 Example of Sculpher's progression of economic evaluation

As may be expected, the progression of research is often not as linear as described by Sculpher's (2006) model (179), particularly in the case of international public health due to the wide diversity of decision making bodies, funding agencies, and epidemiological settings for which research is conducted. An augmented version of this progression is shown in Figure 2. The number of economic evaluations of zinc for child diarrhea is accumulating, and can serve as an example to illustrate the progression of research. The decision problem of whether to advocate zinc for child diarrhea was recognized in the early 2000s leading up to the 2004 WHO recommendation. This recommendation was preceded by a small randomized controlled trial to evaluate zinc paired with copper in a cohort of hospitalized patients (68). This study was followed by a decision tree model using available evidence; cost data from four Tanzanian dispensaries, case fatality rates from a published meta-analysis, and crude triangular distributions to model uncertainty (99). Primary research on randomized control trials were then conducted in the hospital setting in the Philippines (87), and community setting in Haryana India (70). Modeling was then conducted using the interactive Lives Saved Tool (LiST), evaluating zinc with other diarrhea interventions (90). In this dissertation, evaluation of the DAZT program with real world data of a program at scale is conducted using a net-benefit regression to test the cost effectiveness of the program, and different treatment providers, followed by modeling of multiple bundles of interventions with the LiST tool.

4.6 Conceptual framework

A conceptual framework to describe the occurrence of economic costs to caregivers and cost effectiveness can be expanded from literature describing treatment seeking processes. The widely cited socio-behavioral model of treatment seeking for health services by Andersen and Newman (1973) (119) served as the starting point for developing the conceptual framework for this study, with the diagrammatic form of Figure 3, expanding on Shah (151). Treatment seeking is dependent on several interacting variables, including predisposing, enabling, and need factors – and economic costs to caregivers are possible if treatment is sought. Further, the intervention that is provided will be associated with a level of cost-effectiveness.

Predisposing factors include demographic characteristics (household size and sex of the child), characteristics of the social structure (education of the father, education of the mother, and caste), and caregiver knowledge (about ORS and zinc). Enabling factors related to the household included wealth quintile and being part of a financing scheme [having a Below Poverty Line (BPL) card], and related to the community included the main variable of interest (phase of the DAZT program). Need factors included the duration of each diarrhea episode, and having blood in the stool. The source of care (public facility based provider, public community based provider, and private provider) and treatment given (ORS and zinc) are also included. Evidence to justify inclusion of factors both expected to have significant and not significant relationships with treatment seeking, cost, and cost-effectiveness were drawn from the literature and hypothesized directions where evidence specific to diarrhea was not found (Table 2).

Household size

It is expected that expenditures per episode of diarrhea will increase with household size as having more collective resources may lead to higher expenditures per person according to severity. A study from rural Tamil Nadu found that spending on health per capita per year increased with household size (186), and household size is controlled for when evaluating correlates of catastrophic cost and economic cost burden in Bolivia (187). Having additional family members may facilitate taking the child in for treatment, increasing the probability of incurring a cost. Having more children in the house may increase the probability of having an episode as children are a source of infection. However, household size is rarely evaluated when evaluating factors associated with treatment seeking in other literature. It is expected that the odds and amount of costs of the program will be higher, diarrhea frequency will be about the same, and cost-effectiveness will be less favorable with larger household size.

Gender bias

There is a history of preferential treatment for boy children in Asia in the allocation of healthcare resources and timely care seeking (188), and this trend may be exacerbated as women become more educated (189). NFHS-3 evidence suggests that caregivers were more likely to seek care from public facilities for male children, although there was no gender bias in care seeking from private facilities (190). In addition, there was less of a delay in care seeking for male children (191), which may be associated with higher priority and expenditures. An evaluation of cost to caregiver according to child sex in rural Chennai found that caregivers were willing to pay more to protect a male child from an episode ($1.42 for males, and $1.06 for females) (192),[28] although gender bias was less important in the decision to seek care further south in Kerala (193). The GEMS study did not find a significant difference in amount spent on girls compared to boys in Kolkata India (95, 194). A study from West Bengal found that boys received care from qualified health professionals for common illnesses more often and sooner than girls, and more was spent on care for boys (195).[29] It is expected that the odds of having costs and their amount will be lower for female children, although the probability of having an episode would be the same, leading to more favorable cost-effectiveness.

Education

In the Grossman model on the demand for health, it is argued that more educated individuals are more efficient producers of health (196). Mosely and Chen related this concept to child health by suggesting that the education of the mother and father influence care seeking and health care practices (197). More educated parents may be more able to recognize danger signs, understand disease process, and recognize the importance of preventive measures. More educated people often live closer to facilities and are better able to access higher levels of care (198). Less educated people may be more likely to forgo services. Both maternal and paternal education will be included in the models based on the rationale below.

Paternal education: Paternal education was tested as the Mosely-Chen model argues that it influences attitudes and preferences for consumption goods (197), and a father's education plays an important role in earning income. Studies have found a direct relationship between a father's education and access to healthcare. Education of the father was associated with seeking care from a trained provider in Bangladesh (199, 200), and was associated with seeking care at home, a

[28] Inflated to 2013 US$
[29] Illnesses included acute respiratory infection, diarrhea, and fever

pharmacy or vendor, or at medical centers in DHS data from 11 African countries (201). In terms of health outcomes, a greater proportion of deaths was found among children of illiterate fathers than more educated fathers in Bangladesh (202), although paternal education is not associated with stunting (as a proxy for health and nutrition) in Uganda (203). It is expected that probability of incurring costs will be unaffected among fathers with primary education, but higher among more educated fathers. In addition, more educated fathers may influence the mother's preferences to spend more rationally (less on antibiotics and antidiarrheal medicines), and health outcomes will be better, leading to more favorable cost-effectiveness.

Maternal education: Caregivers with some education are expected to be more empowered to seek care and spend on health care more rationally. In India, NFHS data indicate that maternal education was not associated with seeking care (190), but having high school education or above lowered the delay in treatment seeking (204). In addition, only caregivers with higher education were more likely to seek care from providers in general (191). However, the amount of education caregivers had did not affect the proportion with cost or amount of cost in the GEMS study (95). Caregivers with higher education were more likely to seek higher levels of care in China (198). In sub-Saharan Africa, having at least primary education was associated with treatment seeking at home or medical centers, although these caregivers were equally likely to seek care from pharmacies or vendors and traditional healers as people with no education (201). The decision of caregivers for home treatment was attributed to their ability to use health information wisely (201). In Bangladesh, mother's education was not associated with treatment seeking from trained providers (199). Finally, maternal education was associated with more favorable cost-effectiveness of the skilled care initiative in Burkina Faso (111). It is expected that the odds of incurring a cost will be unchanged for mothers with primary education, but those with more education will be more likely to incur costs. More educated mothers will be able to manage costs more rationally and prevent episodes of diarrhea, leading to more favorable cost-effectiveness.

Caste

The Indian caste system consists of scheduled castes, scheduled tribes, and 'other backwards classes'.[30] Scheduled castes are referred to as Dalits (untouchables), scheduled tribes are referred to as Adivasis and are thought of as the original inhabitants of regions of India, and 'other backwards classes' is a term used for other socially and educationally disadvantaged groups that do not belong to the first two categories. Individuals from these marginalized population groups may incur higher costs and have worse health outcomes due to discrimination and other physical, financial, and social constraints to accessing care. For example, children in scheduled castes are less likely to receive immunizations, and mothers are less likely to deliver in an institution (205). Caregivers of children of scheduled caste and other backward classes were more likely to seek treatment for diarrhea and tend to seek it earlier than the other children, although there was no effect for children from scheduled tribes (204). Given that there were differences in significance across these three categories in Malhotra's analysis (204), they will be included as separate variables in the regression analyses. It is expected that scheduled castes and other backwards castes will be less likely to incur a cost and have worse health outcomes, although it is more difficult to predict the effect on the amount of cost or cost-effectiveness. If these caregivers seek care less frequently but have higher expenditures due to the severity of the episode, the average cost per episode could be either higher or lower than the average.

Knowledge of ORS and zinc

Knowledge of ORS and zinc is included as a proxy for program exposure, and may be a factor influencing a caregiver's decision to seek care. NFHS-3 data indicated that lack of knowledge about ORS was associated with seeking care, but did not affect delays in seeking care (191), and it was assumed that the association of knowledge of zinc on care seeking or costs to caregivers

[30] There was no overlap in these three categories in DAZT data

would be similar. It is expected that knowledge of ORS and zinc will be associated with an increased probability of incurring a cost, more rational expenditures by caregivers, and a favorable impact on cost-effectiveness.

Study phase

The DAZT program was expected to lower expenditures on antibiotics and antidiarrheal medicines, and be cost-effective based on a model using cost data from dispensaries in Tanzania (99) and a trial from a community setting in Haryana India (70). An early study from a hospital setting did not find that zinc significantly reduced costs although the expected value for cost-effectiveness was that it was cost saving in terms of reducing the incidence of diarrhea lasting less than or equal to four days (68). A recent study found that zinc and copper were not cost-effective in this setting (85). Since care seeking for diarrhea was predominantly from community settings in the DAZT program, it is expected that the program will show higher odds of incurring a cost, lower total costs, and more favorable cost-effectiveness through time.

Below poverty line card

It is expected that possession of a below poverty line (BPL) card was associated with lower costs and favorable cost-effectiveness as it can defray some of the expense and encourage caregivers to seek treatment. NFHS-3 data indicated that possession of a below poverty line (BPL) card was associated with care seeking for diarrhea (191), although the same dataset indicates that being part of a health scheme or insurance plan was not associated with seeking care from a public or private facility (190). A two-part model on NFHS data found that having a BPL card was associated with lower probability of expenditure for institutional delivery compared to families without one, although differences in the amount spent were not significant (206). Having a BPL card was included to represent financing mechanisms for diarrhea care, and was not considered redundant with wealth quintile as only half of caregivers in the poorest wealth quintile had a BPL card. It is expected that having a BPL card will be associated with a reduced odds of cost, and exempt caregivers from paying fees at public facilities (207), although have little or no effect on amount at private providers. In addition, it may be associated with a higher likelihood of diarrhea episodes, having an unfavorable association with cost-effectiveness.

Wealth quintile

It is expected that wealth quintile would be favorably associated with treatment seeking and cost-effectiveness of the program, although a mixed effect with amount of cost. NFHS-3 data indicate that wealthier caregivers were more likely to seek care and waited less time than those of the poorest quintile (191, 204). A more detailed analysis indicates that wealthier caregivers were more likely to seek care in the private sector, although care seeking from public facilities shows no difference relative to the poorest quintile (190). Wealth quintile had an upside down U-shaped relationship with cost in India in the GEMS study (95). The only available evidence on wealth quintile and cost-effectiveness in LMICs indicates that it has an effect for a skilled delivery care initiative in Burkina Faso (109). Wealth quintile will be included as a series of four variables generated by principal components analysis. The upside-down U shaped pattern observed in Rheingans et al (2012) is expected as households of higher wealth quintiles are more likely to spend more per episode as willingness to pay for treatment is associated with ability to pay, and households of the highest wealth quintile may have mechanisms for saving money. However, it is less clear whether cost-effectiveness is expected to be more favorable as they may also be more effective at preventing episodes from occurring.

Duration of episode

It can be expected that treatment seeking is associated with longer duration of diarrhea as caregivers recognize the need for help in alleviating symptoms. Longer duration of diarrhea was associated with seeking care outside the home in Burkina Faso (208) and Bangladesh (209).

Duration of diarrhea will be included as a continuous variable, and is expected to be associated with a higher probability and amount of cost. As all children with diarrhea have an episode by definition, an unfavorable impact on cost-effectiveness is expected.

Symptoms

It is expected that caregivers of children with symptoms indicating severity will be more likely to seek external care. Number of symptoms of severe illness was associated with seeking care in the Bondo district of Western Kenya (210). In Burkina Faso, clinical symptoms were associated with treatment seeking (fever, vomiting, anorexia) (208). Evidence from Bangladesh indicated that caregivers had the highest likelihood of seeking care when child had respiratory distress, rapid breathing, or had several symptoms at the same time (209). In India, blood in the stool was associated with treatment seeking from private providers (190). Number of symptoms, difficulty in breathing, and fast breathing were tested in our models, although were excluded as they did not lead to convergence. Therefore, blood in the stool is used to represent symptoms as a proxy for severity, and is expected to be associated with higher probability and amount of cost, and less favorable cost-effectiveness.

Place of care seeking and type of care provider

It is expected that higher costs will be associated with private providers since 80% of spending in the private sector is out of pocket (67), where only nominal fees are charged by public providers. In addition, it is expected that costs will be higher at public facilities than public community health workers since transportation costs will be higher and there will be more wages lost. A variable representing seeking care from public facilities will include primary health centers and auxiliary nurse midwives. A variable representing public community based providers will include Accredited Social Health Activists (ASHAs) and Anganwadi workers (AWWs). Finally, a variable representing private providers will include private doctors, nursing homes or private hospitals, mobile clinics, chemists, traditional healers, and charitable, non-governmental organization, and trust hospitals. It is expected that seeking care will have increased odds and amount of cost, and less favorable cost-effectiveness as all children will have diarrhea and incur cost.

Treatment with ORS and zinc

It is expected that being given ORS and zinc will be associated with a higher odds of cost, a higher amount of cost, and less favorable cost effectiveness as all children that receive them have diarrhea.

Excluded variables

Maternal age

It is possible that maternal age would have an important impact on cost or cost-effectiveness as older households may have more financial stability, and that older mothers may be more skilled in managing diarrhea leading to less treatment seeking outside of the home. Indeed, evidence from the National Family Health Survey third edition (NFHS-3) indicated that older mothers were found to have less of a delay in seeking care for their child than mothers under 20 years old (204). However, this data also indicated that age of the mother did not matter for whether care was sought for diarrhea (190), which was confirmed in a survey of four rural subdistricts of Chittagong and Jessore districts (199). No direct evidence exists on the cost of treating diarrhea by maternal age. If good practice can be assumed, it can be expected that prescriptions will be made according to need, and that maternal age will not be associated with cost or cost-effectiveness.

Child age

Studies have found that child age is an important factor in cost of seeking care for diarrhea. Caregivers were less likely to seek care (190) although equally likely to incur direct costs (95) for younger children in India. A study from Nepal found that child age was not significantly associated with treatment seeking (211); and evidence from Bangladesh was mixed between showing no association (209) and caregivers being more likely to seek care from trained health providers for young infants (200). Care seeking from higher level providers was observed for children of younger ages in China (198). In the context of the DAZT dataset, the direction of the effect of child age on cost and cost-effectiveness is not clear. It may not be significant as all patients were infants and it is not expected that older infants will be different from younger infants (similar to 'truncation by Vyas and Kumaranayake 2006) (212). Given this rationale, child age wills be excluded from the model.

Relevant variables that were impossible to evaluate

Breastfeeding

Mothers that breastfed their children were more likely to take them to higher level sources of care relative to those that did not (198). Breastfeeding is associated with incidence and severity of diarrhea (213) and is associated with reduced mortality (4). It is expected that breastfeeding would reduce costs as well as number of episodes, leading to improvements in cost-effectiveness.

Perceived severity of diarrhea

Caregivers can be expected to spend more on episodes of diarrhea perceived to be severe. In Nepal, perceived illness severity was associated with seeking appropriate care, but not timing of care (211). Illness severity was also found to be associated with treatment seeking in Nairobi slums (214). It is expected that our data would show worsened cost-effectiveness with disease severity as more would be spent on more severe episodes, and no analysis will be done on probability of death or long term sequelae.

Distance to health provider

Distance to a health provider can affect a caregiver's decision to seek care due to time, energy, and financial constraints. NFHS-3 data indicated that if distance to a health facility was a major problem, caregivers were less likely to seek care from a public provider (190), although distance was not associated with the timing of care seeking (204). It is expected that the program would be less cost-effective for people living further from health providers.

Living in a rural area

It can be expected that living in a rural area, where health providers are more sparsely distributed, would affect the probability and costs of seeking care. NFHS data indicate that living in a rural area was not associated with the decision to seek care, but rural caregivers wait longer than urban caregivers before taking their child to a provider (190, 204). However, it is not possible to evaluate urban versus rural households as urban villages were excluded from the survey. It is not expected that urban or rural differences would have an effect both in terms of transportation and wages lost as well as user fees.

Living in a deprived neighborhood

It may be expected that caregivers that live in deprived neighborhoods will be less able to access health services, have less money to spend on care, and be engaged in fewer practices to limit the incidence and severity of episodes. Evaluating Demographic and Health Surveys from 11 countries in sub-Saharn Africa, living in a deprived neighborhood was found to be associated with a lower likelihood of seeking care (201). The DAZT study area was chosen as it was underserved by the health system overall; however, the degree of deprivation of individual villages and neighborhoods was not assessed. It is expected that the program would be more cost-effective for individuals in deprived neighborhoods from the perspective that fees may be waived or reduced, although these people may be less receptive to messages about preventing diarrhea or less able to implement them.

Birth order

Birth order can be expected to be associated with treatment seeking and costs as parents may be willing to spend more on their firstborn, and more efficient with their spending for subsequent children. Evidence is mixed about whether birth order is associated with treatment seeking. NFHS data indicate that birth order was not associated with the decision to seek care, or with the timing of care seeking (204). However, caregivers were more likely to seek care from trained providers for firstborn than higher order children in Bangladesh (199). It is not possible to include this variable in our study as information was not collected beyond limiting the survey to the youngest child in the household. It is expected that caregivers would incur lower costs, although diarrhea episodes would be more prevalent for higher order births.

Antenatal care of the mother from trained providers

It is expected that antenatal care of the mother from trained providers makes them more receptive to public health messages such as those from the DAZT program. In Bangladesh, women who received antenatal care were more likely to seek care from trained providers (199). It was not possible to include this variable in regressions as data were not collected in the DAZT program, but would be expected that costs would be lower and cost-effectiveness would be more favorable for women who received antenatal care.

Place of child delivery

Place of child delivery might be expected to be associated with cost or cost-effectiveness, as mothers that deliver in the home may be less likely to seek external care for diarrhea treatment. In India, being born in a public hospital was associated with seeking care from a public or private source (190). It would be expected that the program would be more costly, but also more cost-effective for caregivers that deliver in facilities.

Caregiver working away from the home

Caregivers working away from the home may be less able to take their child to see a treatment provider for diarrhea every time that it is needed, particularly since diarrhea is a frequent occurrence. In the NFHS-3, a caregiver working away from the home was less likely to seek care outside of the home for a child with diarrhea (191). It was assumed that all categories of caregiver occupation except self-employed were away from the home to approximate this binary variable for the regression analyses.

Other variables

Three variables speculated by Gao et al (2012) (198) as being associated with treatment seeking for diarrhea including expected cost of care according to perceived diarrhea status, timing of care seeking, and frequency of diarrhea episodes in the previous two weeks. It is expected that people will spend more for episodes perceived as being more severe, although amount spent will depend more on severity than timing of care seeking or frequency of episodes.

Non-significant variables

Religion

Evidence of the association of religion and care seeking is mixed. NFHS data revealed that Muslims were marginally more likely, Christians were less likely, and Sikhs were equally likely to seek care as other caregivers; although religion did not matter in the timing of care (204), and religion was not associated with choice of public or private care (190). Other studies from India (211) and rural Bangladesh (199) indicate that religion is not expected to be associated with treatment seeking, cost, or cost-effectiveness.

Number of antenatal visits

It might be expected that number of antenatal visits may be related to the value that a caregiver places on medical care. However, evidence from Nepal indicates that number of antenatal visits is not associated with appropriate or prompt careseeking for childhood illness (211).

Number of siblings

It may be expected that number of siblings would be associated with treatment seeking and cost as larger households may have more collective resources to be able to afford care, and older children may be able to supervise younger children while the parent is seeking care for an ill child. However, NFHS-3 data showed that number of siblings was not associated with the decision to seek care, or the timing of care seeking (204). Data on number of siblings was not collected, and it is also expected that this variable would be redundant with household size.

Birth order

Birth order may be expected to be associated with cost or cost-effectiveness as more experienced mothers may be more effective in preventing episodes of diarrhea, and more efficient in managing them. However, the association of this variable with treatment seeking was not significant in India and Bangladesh (199, 211). In addition to data not being collected in the DAZT survey, it is expected that this variable would be redundant with age of the mother.

History of death of a sibling

Having a history of death of a sibling may indicate a lower capacity of being able to care for a child with diarrhea. However, a learning curve may also be possible. No association was found between this variable and treatment seeking in a study in Bangaldesh (199), and no data were collected in the DAZT survey.

5. Methods

5.1 Study information

5.1.1 Setting and study design

Gujarat is in the ‘tribal belt’ of the north of India which, along with Madhya Pradesh and Uttar Pradesh, contributes to half of the diarrhea burden in India (215). 57% of people in Gujarat live in rural areas (20), and most people who live there have no access to a toilet (215). In 2010, the DAZT program was introduced in the 6 districts of Gujarat and 12 districts of Uttar Pradesh (216). Given that the intervention is implemented on a system-wide level, a ‘before and after’ study design was chosen (217), which compares the costs and health outcomes associated with the DAZT intervention with those that preceded the intervention. Outcome indicators include caregiver knowledge, prevalence of diarrhea, treatment seeking, source of care, use of ORS and zinc, cost, and cost-effectiveness.

5.1.2 Data collection

Data collection for the household survey involved surveys at the starting point, midpoint, and endpoint of the study; which were administered to clusters of random samples of households. Each survey elicited information on caregiver’s knowledge of diarrhea management, illnesses in the past two weeks, socioeconomic status, and household data (218). Surveys were administered by community health workers to caregivers in the caregiver’s home. In addition, a provider assessment survey was conducted in 2012 at a random sample of primary health centers (PHCs) to characterize the knowledge and practices of providers with regard to diarrhea and diarrhea treatment. Data on economic costs were obtained prospectively throughout implementation, based on financial records of international non-government organizations working with public and private sector partners to promote and improve access to zinc.

5.1.3 Sampling

The primary sampling unit for the surveys for the cluster randomized sampling strategy was the village. Villages were identified from a 2001 census, excluding urban villages. A village was randomly selected using an index finger, and villages were chosen moving through the list of households until 33 villages were chosen in total. 50 households were interviewed in each cluster, assuming that half would have a child under 5.[31] All households that had a child between 2-59 months old with diarrhea were eligible for the intervention.

5.1.4 Ethical approval

For the main study, ethical approval was obtained from the JHSPH Institutional Review Board to assess scientific merit and allow contact with human subjects. Economic evaluation activities were deemed to be 'not human subjects research'.

5.2 Cost analysis

In Paper 1 of this dissertation, economic costs to caregivers were evaluated with descriptive statistics accounting for the clustered survey design. Principal components analysis was conducted to facilitate evaluation according to wealth quintile in both descriptive statistics and regression analysis. Regression methods were characterized according to a two part model, with logistic regression evaluating the odds of incurring an economic cost, and generalized linear modeling evaluating the amount of economic cost.

5.2.1 Descriptive statistics

Descriptive statistics were calculated according to medians, means, confidence intervals, and p-values reflecting the extent of difference between study phases. Stata svy commands were used to account for clustering with F-tests to evaluate significance in differences between groups.

[31] Average cluster size was 59 in the starting point survey, and 25 in the endpoint survey

5.2.2 Principal components analysis

Principal components analysis was used to categorize caregivers according to wealth quintile using established methods (212, 219). While specific rules do not exist for selecting variables for this analysis, broad categories included durable asset ownership, housing characteristics, and access to basic services based on precedent (219). To avoid illogical rankings (220), only variables with a prevalence between 5%-95% were retained. While these thresholds are arbitrary, they are consistent with rules of general inference to define a value with low probability. Eigenvalues were generated in Stata, which finds linear combinations of variables that capture the maximum amount of remaining uncertainty in the data for each component. The component with the greatest eigenvalue was selected for creating a wealth index, as Filmer and Pritchett argue that higher order components are not important and convention has become to create wealth indices on only one component (219). Factor loadings were assessed to determine what variables aligned the most closely with the principal component, and evaluate whether its representation of wealth had face validity. Caregivers were divided into quintiles, which were used as dichotomous variables for regression analyses. The scale was validated according to a Cronbach's alpha greater than 0.6.

5.2.3 Regression methods

To evaluate economic costs to caregivers, a two-part modeling approach was taken. The first equation used a logistic specification, with a binary variable representing the occurrence of cost as the response variable. Logistic was chosen over probit as its coefficients are more interpretable and the first and second equations are not explicitly linked, which usually requires a normally distributed error term. Coefficients (β) were calculated according to included parameters (x). This sample included all children that received treatment.

$$P(y_1 = 1) = \frac{\exp(\beta_i x)}{1 + \exp(\beta_i x)} \tag{1}$$

Equation 1 was paired with a linear regression to model the amount of cost to caregiver. As various transformations did not achieve a normally distributed error term,[32] and costs had a right skew, the second-part equation on amount of cost used a generalized linear model (GLM) with a gamma distribution and included only the subset of caregivers that had a positive economic cost.[33]

All regression equations account for clustering as testing data indicated that inferences were affected (significance for some coefficients disappeared when clustering was accounted for), and sampling was conducted according to a cluster design.

5.3 Steps to conducting a cost-effectiveness analysis

The cost-effectiveness analyses for the second and third papers were conducted according steps drawn from Drummond et al (2005) (133), Gold et al (1996) (155), and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines (221) – adding calculations of statistical power using equations defined in Glick (2011) (135).

1. Define objectives of the cost-effectiveness analysis
2. Identify audience for the study
3. Determine statistical power
4. Choose analytical approach
5. Define perspective of analysis
6. Describe intervention components
7. Define the counterfactual
8. Define the implementation period
9. Define time horizon

[32] Transformations tested include natural log, reciprocal, square root, and inverse cube root.
[33] Zero inflated Poisson regression is ruled out as costs in econometric modeling are a continuous variable to produce an exact solution. Cost may be treated as a count variable if units of currency are treated as discrete.

10. Choose discount rate
11. Define cost components
12. Define effectiveness measures
13. Choose methods for accounting for uncertainty
14. Define sensitivity analyses
15. Define threshold for cost-effectiveness
16. Describe presentation of results

5.3.1 Objectives of the cost-effectiveness analysis

The research question for the Paper 2 of this dissertation is whether the DAZT program is cost-effective relative to the status quo represented by initial conditions in the area, which is classified by Gold as a 'what is' study (155). Paper 3 evaluates whether bundled diarrhea interventions are cost-effective relative to initial coverage levels in conservative and universal scale up scenarios, representing a 'what if' study (155). These questions will be answered with an aim to inform decisions faced by the Indian Ministry of Health and international funding organizations (154, 222) about strategies for scaling up zinc supplementation for child diarrhea relative to other investment options.

5.3.2 Audience for the study

The audiences for the study include the Indian MHFW, essential drug list and formulary developers, non-governmental organizations, and international funding agencies. The MHFW is developing a HTA organization (169), and these studies will contribute to the body of knowledge available for broadly assessing the public health system. The 2011 National Essential Medicines List currently includes zinc sulfate syrup (58), but dispersible zinc tablets are recommended by the MHFW (59), and the DAZT program used the latter. In addition, zinc is not listed in the National Formulary of India for the treatment of child diarrhea (223). Micronutrient Initiative and FHI-360 may promote the program in other areas with results from this study. Economic evaluation can also guide budget allocation decisions of international funding agencies such as the BMGF, Global Fund, or other overseas aid programs (222).

5.3.3 Power calculation

Equations to determine statistical power and sample size requirements for economic evaluation have been established (134, 135), although are rarely used in the literature. In the case of the DAZT program, as is common for clinical trials literature, sample sizes were calculated for the effectiveness outcome rather than for cost-effectiveness, leaving the option of determining the power with which a meaningful difference can be detected. A distinction between calculating these indicators for a clinical endpoint and for calculating them for a cost-effectiveness endpoint is that instead of comparing outcomes across study arms or phases, the incremental cost-effectiveness ratio is compared to a ceiling ratio. With no established rules about levels of the ceiling ratio for Incremental Cost-Effectiveness Ratios (ICERs) measured in natural units, a wide range of ceiling ratios were considered in sensitivity analysis. In addition, sensitivity of results to variations in other parameters in the formula was tested. Formulas were used to calculate power with different sample sizes and different standard deviations for costs and effects in each phase (adapted from Glick et al (2011) (135) supplementary material) (Box 1). Cost and effect differences and associated standard deviations were drawn from a previous study conducted in Haryana India (70).

5.3.4 Analytic approach

Of the types of economic evaluation available, cost-effectiveness analysis was used to be consistent with other studies in the literature and avoid controversial valuations of health outcomes in monetary terms. For Paper 2, a net-benefit regression was calculated according to methods developed by Hoch et al (2002) (86). The outcome variable in this analysis was the absolute net benefit statistic for each individual patient (i) using cost and effectiveness data from individual patients. To calculate net-benefit, effects (E) were multiplied by the ceiling ratio (λ), to which costs (C) were added. This modification of the net benefit statistic was made since effects were measured in terms of an unfavorable health outcome (episodes of diarrhea), instead of favorable health outcomes that are conventional in the literature to this point.

$$\mathrm{E(NMB_i) = \lambda * E_i + C_i} \tag{2}$$

Program costs were distributed across patients in the intervention phase, and were scaled according to population size and time frame. Using a reference case and series of plausible estimates for λ (section 6.6), columns of net benefit statistics were calculated as the dependent variables for a series of regression analyses.

The next step was to calculate simple regression results for each covariate. The distribution of net benefit statistics was tested for normality, and generalized linear model specifications were used to satisfy regression assumptions since normality did not hold. Covariates included a binary variable (t) to represent treatment (the intervention phase), with its associated coefficient (δ) representing the incremental net benefit of the program.

$$E(y_3 = NMB_i) = \alpha + \delta t_i + \varepsilon_i \tag{3}$$

Additional predictors (β) were added to equation 3 to calculate incremental net benefit controlling for potential confounders.

$$E(y_3 = NMB_i) = \alpha + \sum_{j=1}^{p} \beta_j x_{ij} + \delta t_i + \varepsilon_i \tag{4}$$

Next, a fully-interacted multiple linear regression was formulated, with incremental net benefits for different subgroups of children derived from the treatment variable and interaction terms

$$E(y_3 = NMB_i) = \alpha + \sum_{j=1}^{p} \beta_j x_{ij} + \delta t_i + t_i \sum_{j=1}^{p} \gamma_j x_{ij} + \varepsilon_i \tag{5}$$

In all of these equations estimating net-benefit, the p-value can be used to construct a CEAC. Since p-values given in regression analysis are two-tailed, and one-tailed p-values are needed for constructing CEACs, p-values were divided by two (111). Unadjusted and adjusted CEACs were presented together in the same figure to show the impact of controlling for confounding. These curves were accompanied by tables that present incremental net benefits with p-values showing the significance of the difference from different values of the ceiling ratio. Survey data from the starting point and endpoint of the study were compared as program costs are not available for costs at the midpoint.

Analysis in Paper 3 was conducted using an ingredients approach for costing, outcomes generated with the Lives Saved Tool, and uncertainty accounted for using probabilistic sensitivity analysis. Each of 11 interventions was evaluated independently, as well as in bundles of interventions that could be provided together in the health system.

5.3.5 Perspective of analysis

The cost of the DAZT program is calculated from the societal perspective according to Saving Newborn Lives (SNL) guidelines and standard textbooks (133, 155, 224), to inform broad decisions about the allocation of resources in the health sector. The societal perspective reflects all of the costs and effects affected by the intervention, regardless of who receives them. The main reason for using the societal perspective is that it makes results comparable to others in the literature (155). Costs included are those incurred by implementing agencies, government providers, and households. DALY weights used in the third analysis of this dissertation reflect the valuations of experts at the WHO (225).[34]

5.3.6 Intervention components

Zinc was introduced and ORS use was scaled up to treat diarrhea in children 2-59 months through the Diarrhea Alleviation through Zinc and ORS Therapy (DAZT) program over four years in six districts of Gujarat (Table 1). Health workers and managers in the public sector and pharma reps

[34] Weights according to diarrheal severity have become available in the most recent edition of the GBD study, although our survey did not classify diarrhea according to severity

in the private sector were trained in diarrhea epidemiology, treatment, and product advocacy; and incentives were established to stimulate prescribing and generate demand. Pharmaceutical companies and key stakeholders were convinced to finance and produce zinc, and supply chains were developed to ensure availability of zinc and ORS within communities (226).

Public sector management was provided by Micronutrient Initiative, an international non-governmental organization (NGO) based in Canada. MI worked with the government of Gujarat to develop policies to support the introduction of zinc, and procured zinc using its own tender scheme until the state developed the capacity to procure zinc and ORS on its own. MI organized and managed training of government cadres of health workers including medical officers (MO), auxiliary nurse midwives (ANMs), ASHAs, and Anganwadi workers on use of zinc and appropriate diarrhea management.

Private sector support was led by FHI-360, an international NGO based in North Carolina. The principal providers targeted in the private sector were drug sellers/chemists and rural medical practitioners (RMPs) in rural areas. At facilities, DAZT corners were a key feature of private sector provision, which were staffed informational booths to create awareness and remind providers to prescribe zinc. Key opinion leaders in the medical community and pharmaceutical representatives of local NGOs were trained and supplied with zinc and ORS to enhance further changes in prescribing practices.

In both sectors, each packet of ORS and zinc and referral to higher levels of the health system was recorded by providers, results were communicated to supervisors through SMS messaging, and program reports were validated against data registers. Supportive supervision was provided through monthly meetings, monitoring of field visits, and working with new staff due to high levels of attrition.

5.3.7 Counterfactual scenario

Different approaches to defining counterfactual scenarios have been advocated for economic evaluation including a 'do nothing' strategy for 'generalized cost-effectiveness analysis' (gCEA) to allow the WHO to compare different interventions free from health systems constraints (227). However, a gCEA approach is less useful in a national context as it assumes that budgets can be reallocated easily, which is often not the case. Investment decisions are also made by comparing an intervention to the status quo or next best alternative. The most comprehensive approach to economic evaluation of a single intervention is to compare all pairs of possible interventions (including a 'do-nothing' approach) in an investment algorithm, although this is rarely done in practice (155). The counterfactual for this dissertation was status quo conditions existing at the starting point of the study.

5.3.8 Implementation period

The implementation period for the DAZT program was two years to reflect changes between initial conditions and the program when it was fully scaled up.

5.3.9 Time horizon

The time horizon in the second analysis was assumed to be the same as the implementation period since long term sequelae (cognitive deficits, stunting, obesity, and associated conditions such as cardiovascular disease and diabetes (28)) are not considered due to time constraints of the research. The third analysis had a five year time horizon, reflecting previous work (90), funding cycles such as for the Global Fund (228), election cycles such as for the Lok Sabha,[35] and to be consistent with conventions in other evaluations (90).

[35] http://parliamentofindia.nic.in/ls/intro/introls.htm

5.3.10 Discount rate

Discounting is defined as 'reducing the value of each variable in each future year by an amount that increases the further in the future each year is' (130). The rationale for discounting is that people prefer to receive benefits in the present rather than in the future. All standard texts recommend a 3% discount rate (88, 130, 133, 155), which is the rate of return on 'riskless' investments such as government bonds. Both costs and health outcomes should be discounted at the same rate based on two main arguments: 1) the consistency argument of Weinstein and Stason, and 2) the Keeler and Cretin paradox (155). The consistency argument is that the discount rate for costs and health outcomes should be the same to be consistent with each other, and because it is possible to translate health into wealth and vice versa at any point in time. The Keeler and Cretin paradox states that if benefits are discounted at a lower rate than costs, then implementation of a program will be delayed indefinitely (155). For paper 2, a discount rate of 3% was used to annualize capital costs, and was used to discount recurrent costs projected into the future in Paper 3.

5.3.11 Cost components

Cost components included both program costs for public and private sector NGOs, and economic costs to households. Program costs were divided into capital costs and recurrent costs, with data derived from program records, primary sources, and interviews with individuals responsible for implementation. Capital costs were annualized using figures from Drummond et al (2005). Consumer price indices from the International Monetary Fund (IMF) were used to inflate costs to the current year (229), which were converted to US$ using exchange rates from OANDA.com (230). Incremental government provider costs were derived using reported estimates of time spent on the provision of diarrhea treatment services by public sector providers. Economic costs to caregivers for diarrhea treatment of the episodes in the last two weeks were determined according to data collected through household questionnaire, and consist of direct medical costs of treatment, direct non-medical costs (transportation), and indirect costs (wages lost by caregivers) (95).

5.3.12 Effectiveness measures

In the second analysis, effectiveness was measured in terms of episodes averted as it was impossible to determine which specific children would die given the lack of follow up. In the third analysis, health outcomes were derived from incremental changes in coverage based on DAZT achievements and levels of DPT vaccine coverage expected for other vaccines. These values were inputted into the Lives Saved Tool to estimate the incremental number of lives saved from the study's start in 2011 and linearly extrapolated to 2015 (90). The years of life lost (YLL) component of Disability Adjusted Life Years DALYs was calculated using the standard formula from the Global Burden of Disease study (231). A life expectancy estimate was taken from WHO life tables representing the midpoint between 1-4 years old (232). A discount rate of 3% was used, excluding age weighting to be consistent with the DCPP second edition (130).

5.3.13 Methods for accounting for uncertainty

Methods for accounting for uncertainty include parametric inferences for Paper 2, and probabilistic sensitivity analysis for Paper 3. The first step in probabilistic sensitivity analysis involved defining probability distributions for each input parameter. Beta distributions were appropriate for parameters representing probabilities as they were bounded by zero and one. Gamma distributions were used for cost parameters as they are bounded by zero and have a positive skew. Random samples were drawn from the set of distributions, calculating the total cost, and repeating this process a large number of times. The number of iterations was set at 1,000 according to WHO guidelines, with the rationale that this number of resamples would adequately fill the tails of the outcome distribution (233). Confidence intervals were determined using non-parametric bootstrapping using these stochastic outputs.

5.3.14 Sensitivity analyses

Sensitivity analyses were performed according to different values of the ceiling ratio, and different model specifications in Paper 2 of this dissertation. Paper 3 presented scenarios according to each intervention evaluated individually, the complete bundle of interventions provided together, bundles delivered according to different delivery channels, and different formulations of DALYs.

5.3.15 Threshold for cost-effectiveness

Use of the ceiling ratio is discouraged by some researchers as it can lead to recommendations for uncontrolled growth of new interventions approved in the health sector (234). In addition, cost-effectiveness acceptability curves have been promoted as a means for presenting cost-effectiveness results according to a spectrum of thresholds, allowing decision makers to choose which is the most appropriate for their context (235). However, the case has been made for an explicit definition of the ceiling ratio, and several approaches exist for its formulation (163). Per capita Gross National Income, or some multiple thereof, is a common threshold used in existing literature. Drake has proposed a universal threshold to enhance equity in funding decisions that accounts for the globalization of funding in public health, although a specific definition of this threshold has not yet been attempted (222). Drake proposes that this value could be based on humanitarian principles, a review of historical spending and gains from international aid, a consensus list of widely accepted services, or the per capita GDP of the world's poorest countries (222).

Definitions of the ceiling ratio are only based on weak rationale when cost-utility analysis is used (163), and become even more difficult when cost-effectiveness analysis is conducted using natural units as outcomes. For Paper 2 of this dissertation, an approach to defining the ceiling ratio was taken using outputs from the LiST tool. The per capita GNI of India was multiplied by the number of DALYs per death averted and the number of deaths averted per episodes averted, producing a value of $14.80 per episode of diarrhea averted.

5.3.16 Presentation of results

Results were presented as regression coefficients, net-benefit statistics, and incremental cost-effectiveness ratios with bootstrapped confidence intervals. Cost-effectiveness acceptability curves (235), which plot the probability that an intervention is cost-effective according to different levels of the ceiling ratio, were presented using p-values from regression equations.

5.3.17 Software

Three software packages were used including Stata for descriptive statistics, principal components analyses, and regression analyses; Microsoft Excel using a macro written in Visual Basic for Monte Carlo Simulations; and the Lives Saved Tool to project deaths averted from coverage levels. The Visual Basic macro was adapted from one written by Chris Bombardo for a separate model (236), which has been used in subsequent research (237). There was no need to validate this macro as it relies on standard Excel formulas to perform the Monte Carlo Simulation, and copies results from the stochastic cells to subsequent rows on the spreadsheet.

6. Paper 1

Economic costs to caregivers of zinc and ORS treatment of diarrhea among children under 5 in rural Gujarat India: findings from the Diarrhea Alleviation through Zinc and ORS Treatment program at scale

Introduction: Diarrhea is a leading cause of mortality among young children in India although few receive the recommended treatment. The Diarrhea Alleviation through Zinc and ORS Therapy (DAZT) program was initiated in Gujarat to increase coverage of these interventions through public and private providers at scale. This study evaluates the economic impact of the DAZT program on caregivers of children with diarrhea in the past two weeks.

Methods: The DAZT program evaluation took a before-and-after study design using a two-stage cluster cross-sectional survey. Factors associated with the odds of caregivers incurring economic costs and their amounts were evaluated in a two-part modeling approach.

Results: The DAZT program lowered unadjusted economic costs to caregivers from \$3.71 to \$2.26 assuming the two years of the study. Per million people, costs of diarrhea treatment were lowered by 53% to \$595,898. Controlling for covariates, the program was not associated with a change in odds of incurring an economic cost, and was associated with a reduction in economic cost of \$1.49 (95%CI \$0.17-\$2.80). Cost per person that sought care from private providers was reduced by 40%, particularly among private doctors.

Discussion: Introduction of zinc reduced the economic burden of diarrhea treatment on caregivers in underserved rural areas of Gujarat. Treatment seeking from public community based services both saved money to caregivers and took pressure off of higher levels of the health system. In addition, care was sought more efficiently from the private sector, with an increase in use of private doctors.

Key words: zinc, diarrhea, economic costs, India, Gujarat

6.1 Introduction

Diarrhea is the fourth leading cause of mortality in children under five (238), accounting for an estimated 700,000 deaths globally each year (5). The burden of disease for diarrhea across all ages totals 282,982,000 Disability Averted Life Years (DALYs), which is 11.8% of the total Global Burden of Disease (6). If priority interventions are scaled up to 80% coverage, and immunizations are scaled up to 90% coverage, 95% of diarrhea deaths could be eliminated by 2025 at a cost of $6.715 billion, where no action would result in an additional 1.5 million child deaths per year (239, 240). However, little evidence exists on the economic costs of diarrhea treatment to caregivers in settings where it is needed most.

India accounts for 29% of deaths due to child diarrhea worldwide (5), where one in ten children experience an episode in any two week period (16). However, India is lagging behind in coverage of essential treatments for addressing this burden. Oral Rehydration Salts (ORS) have been available since the 1970s and their use could eliminate 93% of diarrhea mortality (34); however, coverage in India remains low at 26% in 2005/6 (16). National (59) and global (41) guidelines call for the therapeutic use of zinc for the management of acute diarrhea in children under 5, and several meta-analyses indicate that zinc reduces diarrhea duration, severity, subsequent episodes, treatment failure, hospitalizations, incidence, prevalence, and probably mortality (44, 50, 51, 63, 241, 242). However, zinc has yet to be widely introduced and coverage remains at less than 1% in most areas of India (16).

Part of the problem is that there is little investment in health care in India. Average annual public and private health expenditures per capita are $59-$61 (excluding investment in water and sanitation interventions) (14, 243), with 86% of private expenditure being out of pocket (244). In Gujarat, only 3.8% of total household expenditure is spent on out of pocket payments for health services (245). Despite the fact that zinc and ORS cost very little, low expenditures may be indicative of the low priority that caregivers place on seeking care for medical problems, and this neglect can affect households economically.

Prompt and appropriate treatment is important to avoid high costs associated with hospital care and adverse health outcomes. Few studies exist to estimate the costs of diarrhea management and treatment to caregivers in India (95, 246), which may exact substantial economic burden to households when full direct and indirect expenditures are taken into account (inpatient and outpatient medical costs of rotavirus diarrhea are between $41-72 million in India each year (247)). These costs are particularly important among the 68.8% of people living below I$2 purchasing power parity (PPP) adjusted dollar per day who have difficulty financing health care (14). Using a more conservative threshold, 22.3% of people in Gujarat live in poverty, adjusted for health expenditure (245). Even small costs are important to people living in this level of poverty, affecting the economic status of a household and, and having population-level effects given the frequency of diarrheal episodes. In 2004-5, the catastrophic headcount, or percentage of households incurring catastrophic payments (over 10% of monthly income) for healthcare in Gujarat, was 16.76% (CI 15.64%-17.88%) (248).

Several studies exist for comparison of estimates of the costs of managing and treating diarrhea episodes.[36] The Global Enteric Multicenter Study (GEMS) (95) was a community based study conducted across seven countries and included a site in urban Kolkata, which found that caregivers spent an average of $3.65 per diarrhea episode including both direct and indirect costs. Notably, the overall amount of expenditure is lowest among the poorest and richest caregivers. Diarrhea episodes among adults in an urban slum of Mumbai cost $6.89 including transportation, avoidance costs, wages lost, and homemakers' productivity losses (246). In Haryana, caregivers

[36] Costs converted to 2013 US$

spent \$0.83-\$3.38 per diarrhea episode in Faridabad district (70), and \$7.48 in Yamuna Nagar district (249). Zwisler et al (2013) found that caregivers spent an average of \$2.29 per episode out of pocket for diarrhea treatment, mostly for private health worker fees and antibiotics, although it is not clear in which Indian states their study was conducted (73). While data are necessary to better approximate costs at a macro level, assuming a range of \$0.83 - \$6.89 per episode (63, 95) and 312.22 million episodes per year nationwide (5), the economic burden of diarrhea treatment to caregivers in India could range from \$259 million - \$2.34 billion.

Widespread diarrhea management with zinc and ORS has the potential to lessen the economic burden borne by households in India. Evidence the Haryana trial (covering 6 primary health center catchments areas) suggests that these interventions may reduce out of pocket payments by over half through more rational use of medicines and improved health outcomes (70). Work is necessary to better understand the economic burden on caregivers that is associated with diarrhea treatment and the costs of efforts to scale up ORS and zinc at the population level in countries where the burden of diarrhea is high (40).

The Diarrhea Alleviation through Zinc and Oral Rehydration Therapy (DAZT) program was started in 2010 to facilitate the delivery of zinc and ORS through public and private sector providers in Gujarat India (Table 1). In this study, it is hypothesized that the DAZT program lowered the economic burden of diarrhea care to caregivers due to two main factors. Firstly, it is possible that zinc replaced more expensive treatments such as antibiotics and antidiarrheal medications. Antibiotics are prescribed to 80% of patients whether they are needed or not as providers are overly cautious about not neglecting to treat a relevant infection (38), complemented by demand among caregivers for the strongest possible medicine for a potentially deadly episode (73). Secondly, program advocacy may have stimulated caregivers to seek care earlier in the episode, reducing the severity of the case and the likelihood of hospitalization.

6.2 Methods

6.2.1 Study setting and context

This study uses data from the DAZT program conducted between 2010-2013 in 6 districts of northeast Gujarat India (Banas Kantha, Dohad, Panch Mahals, Patan, Sabar Kantha, and Surendranagar – total population 13 million) (20). This area consisted of underserved rural populations in the 'tribal belt' of northern India, which had an infant mortality rate that had declined to 58 in 2005/6 (26).[37] Study sites were chosen due to the high prevalence of diarrhea (13% of children in 2 weeks prior to the 2005/6 NFHS-3 survey (16)), near absence of zinc prescribing, evidence indicating the feasibility of introducing zinc at scale in the two states through collaboration with two international NGOs, and priorities set by the Government of India. Households were included if they were caring for a child of 2-59 months.

6.2.2 Program

The DAZT program was started in 2010 to introduce zinc and ORS through public and private sector providers for treatment of diarrhea in children under five years old. After a decade of negotiations of convincing pharmaceutical companies to produce zinc and building alliances with key stakeholders, policies were developed and supply chains were established to scale up coverage (226). Health workers at each level of the health system were trained in diarrhea epidemiology, treatment, and product advocacy; and incentives were established to generate demand and stimulate prescribers to recommend ORS and zinc. A key feature of private sector provision was the use of DAZT corners, which were staffed informational booths to create awareness and remind providers to prescribe zinc. In both sectors, each packet of ORS and zinc (and referral to higher levels of the health system) was recorded by providers, results were communicated to supervisors through SMS messaging, and program reports were validated

[37] Estimate for rural areas

against data registers. Supportive supervision was provided through monthly meetings, monitoring of field visits, and working with new staff due to high levels of attrition.

6.2.3 Data analyses

Descriptive statistics were calculated accounting for clustering of data by villages using the svy commands in Stata, using a finite population correction according to the number of total episodes. F-tests were used to evaluate statistical significance between phases for continuous variables and proportions not relating to cost. Bootstrapped confidence intervals were calculated for costs since assumptions of normality were violated. Principal components analyses was used to categorize households according wealth quintile using variables including durable assets, housing characteristics, and sources of drinking water (219). The internal consistency of the index, or measurement of whether variables represented entities that were legitimate to combine, was assessed with the Cronbach's alpha coefficient (250), with the threshold for acceptable defined at 0.6. Multivariable logistic regression was used to estimate the effect of covariates on the odds of the average caregiver incurring an economic cost. As opposed to Rheingans et al (2012) (95), this analysis was followed by multivariable linear modeling to assess the influence of these factors on the amount of economic cost. This two-part modeling approach was appropriate as economic costs to caregivers have an excess of zero values (38% at the beginning survey and 40% at the endpoint). Models were specified according to how well they fit the data, compatibility with model assumptions, and ease of interpretation of coefficients.

Covariates tested were chosen from an adapted form of the Andersen and Newman (1973) conceptual framework on treatment seeking behavior (119), as it is expected that economic costs to caregivers will be closely related to treatment seeking, and this model has had influence on several studies in South Asia (251-253). Predisposing factors include demographic characteristics (family size, and sex of the child), characteristics of the social structure (education of the father, education of the mother, and caste), and caregiver knowledge (about ORS and zinc). Enabling factors related to the family included wealth quintile and being part of a financing scheme (having a BPL card), and related to the community included the main variable of interest (phase of the study). Need factors included the duration of the episode and presence of blood in the stool. Theory to support specific variables was based on their significance in previous studies, using treatment seeking as a proxy for cost where literature was lacking. Variables thought to be important were included regardless of whether the coefficient was significant in our data to ensure accurate estimation of variance in coefficients. Parameters where we lacked data were identified as potential sources of omitted variable bias including breastfeeding (198), perceived severity (211, 214), distance to health provider (190, 204), living in a rural area (190, 204), living in a deprived neighborhood (201), birth order (199, 204), antenatal care of the mother from trained providers (199), place of child delivery (190), caregiver working away from the home (191), timing of care seeking (198), and frequency of diarrhea episodes in the previous two weeks (198).

Covariates were assessed according to caregiver report. Maternal education was categorized according to primary (1-8 years), secondary (9-12 years), and tertiary education (13+ years) according to the British structure adopted by the Indian school system (254). Duration of diarrhea was calculated as the difference between the date of onset and date of recovery as reported by the caregiver.

Sensitivity analysis was performed testing the set of covariates affected by the program, including knowledge or ORS and zinc; seeking care outside the home at a public facility, public community based provider, or private provider; and receiving ORS and zinc. Further sensitivity analyses were performed collapsing education and caste variables to single variables, and excluding education. Finally, a sensitivity analysis was performed using only variables included in the GEMS study analysis (95).

6.2.4 Model specification

For the first part of the model, logistic was chosen over probit specification as odds ratios are more interpretable than z-scores, and it is not necessary to link model equations through an inverse Mills ratio (255). Hosmer Lemeshow tests were chosen over Pearson's to assess the goodness of fit of the multivariable logistic model as the number of unique covariate patterns was equal to the number of observations. Results from this test were indistinguishable between logit and probit models, both with p-values < 0.000.

For the second part of the model, several measures were taken to address the positive skew in the response variable. Hospitalized children were excluded due to their high average costs and the influence this had in preventing model convergence. Transformation of outpatient expenditures was tested using natural log, reciprocal, square root, and inverse of the cube root. As quantile-quantile plots (Figure 4) and Shapiro-Wilk tests indicated that none of these transformations normalized studentized residuals, generalized linear modeling was employed.[38] The gamma family was chosen as the distributional form using the Park test (256), and identity link was chosen to represent a direct association between independent and dependent variables (257). A zero-inflated specification was ruled out (257); despite there being two processes – one where caregivers decided whether to seek care, and another whether those that sought care incurred a cost – the interpretation is difficult because some caregivers that decided not to seek care (treated the child at home) incurred costs (e.g. purchase of special food, wages lost).

[38] The sample size for the linear regression was 696, allowing the Shapiro Wilk test to be used

Visual inspection of the residuals versus fitted values plot indicated heteroskedasticity (Figure 5), which was confirmed by a Breusch-Pagan / Cook-Weisberg test ($p<0.000$). In addition, a clustering adjustment was necessary based on the complex survey design of the study. To account for these factors, models were estimated using the vce(cluster vill_code) option. Linearity of the regression line according to continuous variables was tested using Locally Weighted Scatterplot Smoothing (LOWESS) curves in Figure 6, which indicated a potential knot at 6 days of diarrhea duration. As the AIC was lower in the GLM gamma specification with the spline compared to the specification without the spline, the specification with a knot at 6 days was used. Continuous variables were centered at their means to make regression intercepts more meaningful. All calculations were performed in Stata 13 (258).

3.1.1 Power calculation

The main trial was powered to detect differences in coverage of ORS and zinc (assumed to be equal) across trial phases (216, 259, 260). Given a total sample size of 409 that was available from starting and endpoint surveys for GLM gamma regression, power was computed to detect meaningful differences in the economic burden to households across study phases. Data for the calculation was drawn from a previous trial in Haryana India (70) using the standard formula for testing the difference between continuous means (261). The difference in costs between trial arms (Δ) was \$0.67, with a standard deviation of \$0.85 in the intervention arm (σ_1^2), and \$4.17 in the control arm (σ_2^2). With a two sided $Z_{\alpha/2}$ critical value of 1.96 for a 95% confidence interval, and sample sizes taken from the Stata outputs, the $Z_{\alpha/2}$ score that resulted was 0.39 for GLM Gamma regression, giving a power of 65.17%.

6.3 Results

Overall, there were 1,312 episodes of diarrhea among 10,352 children in the two weeks prior to the surveys, although only 486 individuals were included in the analysis. Factors associated with prevalence of diarrhea and seeking treatment will be covered in a separate paper.

6.3.1 Population characteristics, prevalence, care seeking, and wealth indices

All children included in these samples were infants, born to mothers averaging 27 years old, within families of over six people (Table 3). Descriptive statistics indicate some imbalance between study phases, highlighting the importance of controlling for covariates. There may have been a significant reduction in diarrhea prevalence among study infants from 14%-11% from Spring 2011 to Autumn 2013 ($p < 0.000$) (Table 4), suggesting a potential impact of the program, secular trends, Hawthorne effect, or regression to the mean (262, 263). Overall, use of private sources of care decreased with marginal significance from 80% to 74% over the two and a half year period ($p < 0.089$), particularly for nursing homes / private hospitals ($p < 0.000$). Increases were seen in care seeking from community based public sources of care such as ASHAs and Anganwadi workers, which quadrupled their market share by the endpoint of the study ($p < 0.000$). Care seeking from private doctors increased to 64% ($p < 0.067$), in keeping with the overall trend of an increased use of close to client services. In principal components analysis, the distribution of wealth showed a positive skew (Figure 7), and variables selected showed good internal consistency with a Cronbach's alpha of 0.80.

6.3.2 Baseline costs

Before the start of the program, the average cost of diarrhea treatment was \$3.71 (95% CI \$3.03-\$4.39), and the average positive cost was \$5.61 (95% CI \$4.72-\$6.50) (Table 5). The average cost of outpatient visits was \$5.11 (95% CI \$4.26-\$5.95), with the largest components being wages lost, purchase of drugs other than zinc and ORS, and dispensing fees (Table 6). Average cost of inpatient treatment was \$33.09 (95% CI \$10.52-\$55.66) – with the largest components being purchase of other drugs and hospitalizations – and the wide confidence interval resulting in part from being based on only 6 patients. Average cost of home care was \$0.04 (95% CI -\$0.01-\$0.08), with the main components being purchase of special foods and wages lost.

6.3.3 Costs by source of care seeking

The source of care seeking was an important factor associated with economic cost to caregivers. Compared to the average total economic cost at the endpoint of the study, private doctors, and nursing homes and private hospitals were particularly costly at \$3.81 and \$8.27 per caregiver respectively ($p < 0.000$) (Table 7). Costs among caregivers consulting Anganwadi workers were significantly less than average expenditure at both starting point and endpoint surveys. Caregivers in the poorest quintile incurred lower costs than other quintiles ($p < 0.013$ at the endpoint of the study), suggesting either progressive financing or inefficient patterns of forgone treatment when costs were expected to be high.

6.3.4 Variables associated with the odds of incurring a cost

The DAZT program was not associated with a change in the odds of a caregiver incurring an economic cost from the starting point to endpoint of the study ($p<0.75$) (Table 8), which held when tested according to covariates included by Rheingans et al (2012) (Table 10) (95). Important influences on the odds of incurring an economic cost to caregivers included duration of diarrhea, treatment by a public community based provider, and treatment by a private provider. Each additional day of diarrhea under 6 days was associated with 76% higher odds of an economic cost (95% CI: 19%-159%). Receiving care from a public community based provider was associated with a 92% lower odds of incurring a cost (95% CI: 76%-97%). Receiving treatment from a private provider was associated with higher odds of a caregiver incurring an economic cost by a factor of 37.8 (95% CI: 12.0-119.3). In sensitivity analysis, duration of diarrhea <6 days was robust at the $p<0.02$ level, and receiving care from a public community based provider or private provider were robust at the $p<0.01$ level (Tables 9 &10). Paternal primary education and being given zinc were marginally associated with odds of incurring a cost in reference case calculations, but these results were not robust to all sensitivity analysis.

6.3.5 Changes in cost over time and influences on amount of cost

A reduction in economic costs to caregivers from \$3.71 to \$2.26 was achieved across all children that had diarrhea in the past two weeks from starting point to endpoint surveys (Table 5). For caregivers with a positive cost (as a proxy for seeking treatment outside of the home), a larger reduction was achieved (\$5.61 to \$3.73). The cost of outpatient care decreased from \$5.11 to \$2.98 per caregiver (Table 6), or by \$1.49 (95% CI: \$0.17-\$2.80) for the average caregiver controlling for other covariates in GLM Gamma regression (Table 9). Reduction in indirect costs (wages lost) was the most important reason for this decline, although reductions in transportation costs and expenditures on drugs besides zinc and ORS were also observed (Table 6, Figure 8). Dispensing and purchase of drugs other than ORS and zinc accounted for the largest share of direct costs. Notably, expenditures on ORS and zinc were very small fractions of the total.

Each additional day of diarrhea and seeking care from a public facility or private provider were associated with an increased cost (Table 11), which was robust to sensitivity analysis (Tables 10 & 12). Knowledge of ORS among caregivers improved ($p<0.000$), interpreted as a proxy for exposure to program messages, and was associated with a decrease in cost in most model specifications.

Unadjusted analysis indicated that the largest reduction in cost among provider types was among private providers across the span of the program (Table 5). However, the relative importance was not seen when adjusted for covariates ($p < 0.196$). Instead, a reduction in costs across the trial among public community based providers relative to those among other caregivers was observed ($p < 0.014$).

Mothers having lower costs may have been associated with lower costs, although significance depended on the model specification. Knowledge of zinc had no effect on amount of cost controlling for other covariates, and administration of zinc was only marginally associated. In addition, this study did not find evidence of gender bias in terms of expenditures on diarrhea treatment.

Results according to wealth quintile suggest that expenditures were reduced across study phases in all but the least poor quintile (Table 5). These quintiles were defined by variables that had the strongest correlations with the unrotated first principal component (assumed to represent wealth). Variables positively associated with wealth included piped water (factor loading = 0.2231), pit slab latrine (0.2437), cooker (0.2483), and color television (0.2466). Variables with the strongest negative correlations were open space latrine (-0.2360) and dung floor (-0.2874). However, while these factors deserve attention when assessing the equity impact of the program, universal coverage should be emphasized over using these factors to define targeted financing schemes or provision of these inexpensive and potentially life-saving medicines.

6.3.6 Costs of hospitalized patients

Among the 13 hospitalized patients that were observed across surveys, there was a significant difference in economic costs to households between the starting point and endpoint of the study (Table 6). A particularly expensive patient increased the cost of admission/hospitalization at the midpoint of the study, costing 9,968 rupees ($167.89). The top 10% of caregivers incurred a cost of $10.31 at the starting point (95% CI $8.45-$11.91), $9.86 at the midpoint (95% CI $8.05-$12.98), and $6.96 (95% CI $6.23-$7.75) at the endpoint of the study; indicating that the intervention may have reduced the burden of high cost patients. Boxplots suggest that outliers may have been reduced at the study endpoint, and occurred mainly at private sources of care, specifically private doctors and nursing homes/private hospitals (Figures 9 & 10), although the significance of this result is not confirmed with hypothesis testing. Outliers were also observed among higher wealth quintiles, suggesting a possible association with ability to pay, although this finding also was not tested for significance.

6.3.7 Costs among caregivers that provided home treatment

Costs among caregivers that treated their child at home mainly consisted of wages lost. No expenditures were made on zinc or ORS, and no changes in economic costs were observed across study phases among these caregivers.

6.3.8 Population level costs

Overall, diarrhea treatment seeking cost caregivers between $595,898-$1,777,522 per 1 million people across one year (Table 13). An increasing preference for outpatient care was observed across phases, contributing to a reduction in cost per million. In total, outpatient care accounted for the bulk of the economic burden to caregivers, although infrequent but expensive hospitalizations can have a substantial impact on total costs, as seen in the hospitalization costs at midline. These outliers are important enough to interrupt the downward trend suggested in Table 6.

6.4 Discussion

Studies evaluating economic costs to households of health interventions are essential for setting priorities in public decision making, predicting levels of demand, and providing data necessary for subsequent cost-effectiveness calculations from a societal perspective. This study assessed direct and indirect economic costs associated with diarrhea treatment before and after the introduction of the DAZT program in Gujarat India, finding reductions in indirect costs (wages lost), transportation costs, and amount spent on medicines besides ORS and zinc. While it was not possible to assess whether delays in care seeking were reduced, results support the hypothesis of this study that cost savings would be achieved through reduced antibiotic and antidiarrheal use, and also suggest reductions in expenditures due to more efficient care seeking in the health system. Use of community based services increased (ASHAs and Anganwadi workers), use of efficient private sector providers increased (private doctors), and use of higher level sources decreased (nursing homes and private hospitals). These findings are both plausible and amenable to intervention. Besides findings from this study, evidence supporting the feasibility of a community based health systems strategy for treating diarrhea is proliferating through the Strengthening Health Outcomes through the Private Sector (SHOPS) initiative in a variety of settings, highlighting Sierra Leone, Guyana, Malawi, and Bangladesh (40).

Results suggest that the proportion of caregivers that incurred an economic cost at the initial survey (62%) and endpoint survey (60%) was lower than that found in another study from rural India (79%) (73). A pilot study from Haryana found that the percentage of caregivers incurring a financial cost decreased from 97% to 70% (96), possibly reflecting a setting with greater potential for reduction in the occurrence of these costs. However, reducing the proportion of caregivers that incurred a cost may not be favorable from a policy perspective as an increase in the proportion may indicate that more caregivers are seeking and receiving appropriate care for their child. The desired trend was seen in Bangladesh, where an increase in the proportion of caregivers that incurred a cost per episode of diarrhea was observed, with a decrease in the amount spent (95).

Putting economic costs into context, $2.26-$3.71 for average economic costs is a bit more than the daily minimum wage in Gujarat (133 rupees, or $2.24).[39] Results compare to similar studies reviewed in the introduction of this chapter, and related studies have been conducted in Pakistan and Mali. In a comprehensive program introduced in Pakistan in 2005, a training, provision, and

[39] http://www.paycheck.in/main/salary/minimumwages

marketing strategy was implemented through facility and community based levels of both the public and private components of the health system (71). This program lowered household costs by 12.8% ($0.50) (71). In a program in Mali introduced in 2006, zinc and ORS were provided at first level facilities which distributed drug kits to community health workers. This program increased ORS use rates by 10% to 43%, doubling sales levels in the community, at minimal mean total cost to households (72).

The difference in proportions of children who were hospitalized across phases was not statistically significant. The average total cost for these inpatients ranged from $8.32-$77.16 across phases, which is 0.56%-4.67% of per capita GNI (14). These results compare to $25.18 per patient in a hospitalized cohort in Nagpur, although the estimate from that study includes costs to the government in the total (85). The small number of datapoints in our sample produces large standard errors, and there is a scarcity of studies in the literature, making precise comparisons difficult.

Diarrhea prevalence may be an overestimate as all children in this analysis were infants, and incidence peaks between 6 to 11 months (4, 8). In comparison to published estimates, prevalence was comparable to levels reported in the 2005-6 National Family Health Survey – 13% in Gujarat (26) – however this estimate precedes our study by half of a decade, and state wide prevalence levels may be falling due to secular trends and economic development. Total costs including non-drug components are affected by low probability, high cost episodes, which were not seen in the endpoint survey of the DAZT program. While outliers appeared among caregivers of higher wealth quintiles, these results may have been due to chance, and should not mask the fact that people of lower wealth quintiles may be forgoing treatment of serious cases and bearing the burden of premature mortality. Nasrin et al (2013) suggest that reasons that caregivers do not seek care is usually because they don't consider the illness to be severe enough to warrant treatment

(92%), and 100% of those that do think that care is needed cite cost as a reason for forgoing treatment (264).

In agreement with our findings, the GEMS study highlighted the importance of the influence of diarrhea duration on odds and amount of economic cost per episode (95). This result is logical as duration and severity may be correlated, leading to treatment seeking and increased amount of care. The finding that private providers are associated with higher costs is relevant as nearly 62%-74% of caregivers seek care from private or unqualified providers in Gujarat and 80% of spending at private providers is in the form of out of pocket payments (67, 246). As opposed to an evaluation of NFHS data by Malhotra et al (2013) (191), and a contingent valuation study evaluating differential willingness to pay for treatment among caregivers of male and female children in Chennai (192), no evidence of gender bias was found in our study. This finding is corroborated with the lack of evidence for gender bias in Kolkata in the GEMS study (95).

A strength of this study is in the level of detail on economic costs to households in a rural area, which is unique except for a previous study from Haryana India (63). A similar dataset is being generated from a site in Uttar Pradesh, and being conducted in two study sites with important epidemiological and health systems differences will allow questions of generalizability to be addressed. Finally, significant differences in adjusted cost were detected despite being underpowered to detect meaningful changes in cost at the 80% level, assuming values from the Haryana trial. This finding adds strength to the result that a significant change exists.

It was difficult to assess severity of episodes directly, and principal components analysis to summarize information from symptoms interfered with the convergence of the maximum likelihood estimation of our regression equations. Similarly, the generalized linear model (GLM) regression with a gamma distribution failed to converge for midpoint to endpoint comparisons.

Pregbion's link test was significant for both the multivariable logistic and GLM gamma reference case models, although variables justified in the reference case were included to ensure that variance was not underestimated.[40] Caregivers were not asked to identify the types of antidiarrheal medicines or antibiotics given, and dosages were not assessed to account for changes in prescribing patterns or adherence. Demographically, only rural areas are represented; however, these are the main areas where zinc availability should be improved (38), and universal coverage is recognized as priority by the Indian Government (42). The long term impact of the program on households or the epidemiological profile of the study area are not assessed, and the series of cross-sectional surveys does not capture reasons why costs changed through time or if changes occurred with repeated episodes.

No information was collected on the sources of financing, although 48% of households used savings in the GEMS study, and other major sources included borrowing (21%), cutting other expenses (21%), and reducing the number of meals (19%) (95). Information on the use of coping strategies (aka distress financing (265)) would be helpful to develop solutions to address questions about affordability. To calculate the proportion of households that incur catastrophic health expenditures (266), information on monthly household expenditure on food and non-food items is necessary. Finally, information was not collected on the use or cost of any diagnostic tests, costs of obtaining or purifying additional water, or the monetized value of household tasks left undone while caregiving (95, 246).

6.5 Conclusions

This study evaluates the impact of the DAZT program on economic costs of treatment of child diarrhea to caregivers in rural Gujarat India using a two-part modeling approach that has not yet

[40] Sensitivity analysis using the set of variables specified by Rheingans et al (2012) gave a non-significant coefficient for y-hat squared in Pregbion's linktest for logistic regression, but the coefficient remained significant for GLM gamma in this specification.

been applied to this area of research. It is important to understand these costs as the burden of diarrhea is high, both in terms of frequency of episodes and in terms of mortality, and since even the low costs of treatment can be problematic for people living in poverty. The main finding was that costs were reduced both through improving rational drug use and through improving rational access of the health system. Antibiotics, which are appropriate only with bloody diarrhea or shigellosis, and antidiarrheal medicines, which can be harmful and should not be prescribed, were prescribed more frequently but expenditures on them were reduced. Use of public sector providers increased, with care seeking from community based providers increasing four fold. In addition, care seeking from private providers was reduced, the amount caregivers paid who accessed them fell, and caregivers that used the private sector were more likely to access private doctors. Despite the fact that diarrhea treatment is usually not expensive, the frequency of episodes and reduction in prevalence translate to a large overall cost savings to the health system through effective treatment. Episodes of long duration, and caregivers that access private providers should be targeted by intervention programs, particularly with an aim to strengthen close to client services. Despite adding a small cost to diarrhea treatment programs, scaling up zinc can lead to health systems efficiencies, and is likely to be cost-effective in this context.

7. Paper 2

Economic evaluation of the Diarrhea Alleviation through Zinc and oral rehydration Therapy (DAZT) program in rural Gujarat India: an application of the net-benefit regression framework

Introduction: Net benefit regression is a valuable analytic technique for economic evaluation of nonrandomized study designs; however, it has been rarely applied in a low- and middle-income country context. The purpose of this study is to evaluate the Diarrhea Alleviation through Zinc and oral rehydration Therapy (DAZT) program for scaling up treatment of child diarrhea in rural northeastern Gujarat India relative to status quo conditions.

Methods: Data was drawn from starting point and endpoint surveys of an evaluation with an uncontrolled before and after study design. The power of detecting a significant difference in net benefit in this dataset was calculated using published methods. Costs were evaluated from a societal perspective, including program costs for both public and private sectors and economic costs to caregivers, with effectiveness assessed in terms of episodes of diarrhea averted. Three model specifications were tested including simple regression with the phase variable alone, multiple regression with the complete set of covariates, and regression with the full set of covariates and each interacted with the phase variable. To account for non-normal error terms, models were specified with generalized linear modeling with a gamma distribution. Cost-effectiveness acceptability curves were calculated for all three specifications. Subgroup analysis was not emphasized due to policy reasons why targeting zinc is not advocated as a health systems strategy.

Results: The DAZT program had sufficient power to detect a meaningful difference in incremental cost effectiveness relative to the expected policy maker's valuation of averting an episode of child diarrhea (λ). The fully implemented program was dominant (lower cost with

fewer episodes of diarrhea) relative to status quo conditions with 100% certainty in the unadjusted and adjusted models, and was cost-effective with over 95% certainty in the fully interacted model.

Discussion: This analysis indicates that the DAZT program is likely to be cost-effective relative to the status quo condition depending on which covariates are included in the model. However, results should be interpreted cautiously given the lack of control group in the program evaluation. Net benefit regression is a promising analytical technique for evaluating studies with non-randomized designs evaluating interventions relevant to low- and middle-income country health systems. Modifying the net benefit statistic to allow for 'health gap' measures makes possible the use of econometric specifications not yet applied to net-benefit regression such as Generalized Linear Models (GLMs) with a gamma distribution.

7.1 Introduction

7.1.1 Cost-effectiveness analysis

Cost effectiveness analysis (CEA) is a useful tool for improving allocative efficiency in the health sector (133), and has been widely applied, particularly in publicly financed health systems. In India, public sector spending is particularly low, although has been expected to increase (67, 147),[41] and evaluation is necessary to ensure that resources are employed efficiently to help achieve goals for universal access to health care (267). In addition, economic evaluations of interventions delivered mainly through the private sector can improve health systems where private provision is predominant (268), even if the set of evaluations are not considered in a systematic way. Further, India is a recipient of large amounts of international development aid, and despite the absence of formal prioritization mechanisms, donors face pressures to fund and help implement interventions that are cost-effective (154). Finally, economic evaluation of health systems models found to be cost-effective in India may help its government prioritize investments to help other countries through its own burgeoning international aid program (267).[42]

Economic evaluation in countries with strong traditions of health technology assessment often follows a general continuum from modeling studies to evaluations alongside clinical trials, which can in turn inform revisions to make models more comprehensive (179). Less attention has been paid to economic evaluation in the context of implementation science and non-randomized study designs. Methods have been developed recently which combine econometric and economic evaluation techniques through transforming incremental cost-effectiveness ratios into net benefit statistics (86). Net benefit regression allows analysts to control for variables that may confound cost-effectiveness when allocated unevenly across scenarios being compared.

[41] The goal of the Indian government is to increase health spending to 2% of GDP (Berman et al 2010)
[42] India allocated $680 million in 2010 to foreign assistance programs and is a net-exporter of pharmaceuticals (Watt et al 2013)

7.1.2 Diarrhea in India and DAZT program

The Diarrhea Alleviation through Zinc and oral rehydration Therapy (DAZT) program in Gujarat India is an example where net benefit regression is applicable in a low- and middle-income country (LMIC) context. The objective of the DAZT program was to scale up coverage of oral rehydration salts (ORS) and zinc for treating children with diarrhea, and reduce the irrational prescription of more expensive antibiotics and antidiarrheal medicines. Program evaluation took a before and after study design across 2010-2013, and the intervention consisted of a complex health system wide approach through which zinc was introduced and ORS was scaled up through both public and private sector providers. This design allows for the evaluation of zinc itself as an intervention, as well as evaluation of the health systems delivery strategy.

7.1.3 Literature review

The application of net benefit regression in a LMIC context is relatively new. Hounton and Newlands (2012) (109, 111) conducted the first two studies to evaluate public health interventions in a LMIC context, including programs for skilled attendance at childbirth and community based insurance in Burkina Faso. Shih (2009) published a net-benefit regression analysis in 2009 relevant to Taiwan (269), which is technically a LMIC since it is part of China, although is considered a high income region by the World Bank (270). In addition, cost-effectiveness analyses of before and after studies are emerging (102-107); however, these studies are not well established in the literature.

Cost-effectiveness studies relevant to the introduction of zinc to treat child diarrhea include a model based analysis (99), hospital based studies that use patient level data (68, 85, 87), and a community based study based on patient level data (70). Consistent with WHO recommendations (271), zinc has been found to be cost-effective for treatment of non-severe cases based on modeled evidence (99), a community based cluster randomized trial evaluation (70), and an evaluation of a social franchise program (132); but not cost effective (85), or without significant differences in effect (68, 87) in the hospital setting. Further work should be done to evaluate cost-effectiveness in real world sector-wide conditions to inform decisions about scaling up zinc to achieve high levels of coverage. This information is particularly relevant in the Indian context where the government has set policy for a national program to provide zinc to all children over three months old with diarrhea (42), and diarrhea was the third leading killer of children under five years old nationwide in 2010 (272), although its rank has fallen from second to fourth worldwide in the last few years (238).

7.1.4 Study hypothesis and rationale

The hypothesis of this study is that the DAZT program was cost-effective relative to status quo conditions for treating diarrhea in rural Gujarat. The DAZT program was designed according to lessons learned from similar successful programs, such as the SUZY program in Bangladesh, and the 'status quo' counterfactual was chosen to inform marginal investment decisions (155). Chapter 6 found that the prevalence of diarrhea among infants may have been reduced from 14% to 11%, in addition to lowering the economic burden borne by caregivers across the span of the program (273). Consistent with economic evaluations of other interventions delivered at the community level (274, 275), it is expected that program costs will be distributed thinly enough across beneficiaries of the program to make economic costs per person good value for money when considered alongside health benefits.

Reviews of effectiveness literature suggest that zinc efficacy is modified by a variety of variables (51, 131), and interventions delivered at scale may benefit some subpopulations more than others given inequities in coverage of child health services. In Gujarat, coverage of maternal, newborn, and child health is 32.4% among people in the poorest wealth quintile, and twice that in the richest quintile (276). For the effectiveness of zinc, Patel et al (2009) recommend that 'a reexamination of all available trial results … is needed to dissect out the potential contributions of heterogeneity of trial results before Zn can be recommended universally' (131). Lazzerini and Ronfani (2013) have addressed this question recently in terms of efficacy and effectiveness (51), and the question exists whether similar work should be conducted on cost-effectiveness. Given the standards of the National Institute of Health and Care Excellence (NICE) for subgroup analysis (277), and plans of the Indian Government to develop a similar organization (169), the case can be made that evaluation of the cost-effectiveness for different subgroups is particularly relevant from a policy perspective. However, countering this rationale is that zinc should not be targeted to specific subgroups as it is likely to slow the development of drug resistance to antibiotics instead of contribute to drug resistance through widespread use as has been seen for malaria and pneumonia programs (278). In addition, taking a targeted approach rather than universal coverage may introduce inefficiencies in trying to administer the rationing strategy in the health system (67).

7.2 Methods

7.2.1 Study setting

The DAZT program was implemented in the context of India's largely private health system, utilizing community health workers, dispensaries, chemists, primary health centers, hospitals, and other sources of health care. The study area consisted of six districts in northeastern Gujarat (Banas Kantha, Dohad, Panch Mahals, Patan, Sabar Kantha, and Surendranagar – total population 13 million (20)) which are currently underserved by India's health system. The study area was chosen for its low coverage of zinc, availability of non-governmental organization partners, and priorities set by the Government of India. Evaluation of the DAZT program consisted of household surveys spanning two years comparing 5,080 caregivers of children 2-59 months in the final survey to 4,200 children assessed at the beginning (Table 14). These surveys assessed only the youngest child in the household, and the latest episode per child within the last two weeks.

While it was not possible to extrapolate long term outcomes from patient specific data on episodes of diarrhea, data was sufficient to perform cost-effectiveness analysis in terms of natural units.

7.2.2 Power calculation

The main trial was powered to detect differences in coverage of ORS and zinc (assumed to be equal) across trial phases (216, 259, 260). Given the sample sizes that were collected in program activities (Table 14), power was computed to detect meaningful differences in cost-effectiveness, translated to incremental net-benefit (Box 1).

Power associated with cost-effectiveness was calculated merging two formulas from Glick et al (2011) ((135) supplemental material) to account for different sample sizes across study phases, and different standard deviations in costs and effects across phases. Alternative hypotheses were tested against a null hypothesis of no difference of net benefit from a ceiling ratio (λ), or a policy maker's willingness to pay for diarrhea treatment. A novel calculation was conducted for the reference case of λ based on outputs from the Lives Saved Tool (LiST) by multiplying per capita GNI ($1,653) by DALYs averted per death averted (27.06), and deaths averted per episode (1,082/3,269,219). This calculation produced an estimate of λ = $14.80 per episode averted.

The reference case power available by the study sample size and sensitivity analyses are given in Tables 15 & 16. Values for ΔC, ΔQ, and their standard deviations were taken from a trial on zinc conducted in Haryana India (70). The expected correlation (ρ) between incremental cost and effect was assumed to be 0.2 based on convention for sociological studies. The standard Z score for 95% confidence was used for a two-tailed alpha (1.96), with sensitivity analyses on 99%, 90%, and 80% confidence. Results indicate that halving effectiveness reduces power, and reducing effect to 0 provides power to detect a difference in the direction of not being cost effective. Reducing cost increases power to 100%. In addition, Z_β scores reach their lowest point where net benefit equals zero (when the ceiling ratio equals $7.64). Power reaches its lowest point (α) at the same point (Figure 11). The correlation coefficient has little influence on power, and power decreases with increasing α. Figures 12 & 13 show the relationship between λ and power.

7.2.3 Costs and effects

Economic costs were assessed from the societal perspective, consisting of those to the caregiver and program costs borne by the NGOs and government. Program costing was performed according to Saving Newborn Lives (SNL) costing guidelines for capital and recurrent costs (224). Data were drawn from program records. Costs to caregivers were assessed according to caregiver report through the household surveys, and included direct medical costs, direct non-medical costs (transportation), and indirect costs (wages lost).

Program costs were combined for public sector and private sector activities (Table 17), and were divided evenly across caregivers in the endpoint survey. A full year of program costs at the midpoint survey were not available, limiting capacity to evaluate cost-effectiveness at that stage of the program. Allocation of program costs across caregivers was scaled to the population of children in the study area (n = 1,188,634), and according to time frame (2/52 weeks) to consider coverage of children beyond the scope of the surveys. Program costs components included capital costs (start up and sustainability, furniture and equipment, and training), and recurrent costs (personnel, vehicles, buildings, zinc and supplies). Capital components were annualized using factors from the WHO-CHOICE study discounted at 3% as the rate for a risk-free investment (155) and recommendations for economic evaluation in LMICs (88). In the absence of other data, items were assumed to last the duration of the program. Currency was inflated using consumer price indices from the International Monetary Fund (IMF) and converted using factors from OANDA.com.

In the absence of data on mortality and long term sequelae from diarrhea, outcomes were assessed in terms of episodes averted. No attempt was made in questionnaires to define diarrhea according to official WHO definition (279). Evaluation was limited in its scope to the most recent episode per child within the two weeks prior to study to limit recall bias.

7.2.4 Traditional cost-effectiveness calculation

The cost-effectiveness of the program was calculated according to the costs and episodes averted observed in the trial. In a separate study (280), uncertainty around these estimates will be defined using a non-parametric bootstrap according to established methods for cost-effectiveness analysis (133).

7.2.5 Cost-effectiveness according to net benefit regression

All children evaluated by starting point and endpoint surveys of the study were included. For each individual, a modified version of the net benefit statistic was calculated by multiplying the variable representing whether a child had an episode of diarrhea by the value of averting an episode (λ), then adding the economic costs associated with that individual.

$$E(y = NMB_i) = \lambda * E_i + C_i \tag{6}$$

A modified version of the incremental net benefit can therefore be represented by the number of episodes averted between the study starting point and endpoint, and by the same difference for costs.

$$NMB = \lambda * (Eb - Ee) + (Cb - Ce) \tag{7}$$

This analysis was different from the typical net benefit statistic of most net-benefit regressions (86, 109, 111) in that episodes of diarrhea are an unfavorable outcome, where other outcomes used (e.g. days of stable housing (86), enrollment in community based insurance (109), institutional delivery (111), successful diagnosis (110)) are favorable outcomes. To ensure that the incremental net-benefit statistic had the appropriate sign, individuals assessed in the initial survey were coded 1 and those assessed in the endpoint survey were coded 0. Coding of other variables was inverted in the same way. As both episodes and costs are unfavorable, adding them within trial phases was appropriate before taking the incremental difference between the two. With more episodes observed at the starting point of the survey, the value of incremental benefits was positive in this formulation. The sum of program costs and economic costs to caregivers was observed to be higher at the endpoint than starting point of the survey, so the resulting incremental cost was subtracted from the incremental effects. When the sum of costs and outcomes converted to dollar values are higher at the starting point than endpoint of the survey, incremental net benefits are positive, producing the correct interpretation for policy.

The net benefit statistic was used as the dependent variable in a series of simple and multivariable linear regressions. In these formulations, the coefficient on the treatment variable (δ) represented incremental net benefit of the program relative to the initial survey. Simple linear regression on the δ alone, representing study phase, was conducted to show that the incremental net benefit is the same when calculated in this approach as when calculated in the standard deterministic approach.

$$E(y = NMB_i) = \alpha + \delta t_i + \varepsilon_i \tag{8}$$

Multiple linear regression was then conducted to evaluate net benefit when controlling for covariates (x_{ij}).

$$E(y = NMB_i) = \alpha + \sum_{j=1}^{p} \beta_j x_{ij} + \delta t_i + \varepsilon_i \tag{9}$$

Finally, marginal net benefit was calculated by interacting each parameter with the treatment variable (γ).

$$E(y = NMB_i) = \alpha + \sum_{j=1}^{p} \beta_j x_{ij} + \delta t_i + t_i \sum_{j=1}^{p} \gamma_j x_{ij} + \varepsilon_i \tag{10}$$

Different values of λ were tested in sensitivity analysis, including the extreme case of 0 to test negative costs as the response variable. An effects only regression to represent the scenario where λ equals infinity was not conducted as the outcome is binary and logistic regression coefficients would not be comparable to other model specifications.

7.2.6 Cost-effectiveness acceptability curves

Cost effectiveness acceptability curves (CEACs) were constructed to depict the probability that the DAZT intervention was cost-effective according to different levels of λ using p-values on the treatment variable. Stata outputs for results above the threshold were subtracted from 1 and all outputs were divided by two to convert them to one-tailed tests. Similar to comparisons of coefficients, results from simple linear regression and multiple linear regression were compared to assess the effect of controlling for covariates on the position of the CEAC.

7.2.7 Regression modeling

It was expected that ordinary least squares estimation would not be a good fit given the skewness in the outcome variable, although it is difficult to test normality of residuals in large datasets.[43] Therefore, a quantile-quantile plot was generated, which illustrated this right skew (Figure 14). Breusch Pagan / Cook Weisberg tests indicated that the residuals did not have constant variance at different points along the regression line, and visual inspection of residual versus fitted plots in Figure 15 a-c confirmed heteroskedasticity.

As another check on these model assumptions, models were specified comparing OLS, negative binomial, and GLM gamma with Akaike's Information Criterion (AIC) and the Bayesian

[43] The Shapiro Wilk tests performs well in sample sizes up to 2000, the Shapiro Francia test performs well in sample sizes up to 5000, and the Jarque Bera test does not perform well in large sample sizes. The skewness and kurtosis test did not produce results in this dataset.

Information Criterion (BIC), which indicated that GLM Gamma was clearly the best fit, even up to λ of $1 million.[44] Of the generalized linear model options for error term distribution (257), Gamma family was appropriate as data were non-negative, continuous, and skewed (Figure 13).[45, 46] Identity link was prioritized to preserve correct interpretation of the coefficient on the treatment variable, although suffered from convergence problems. Therefore, relationships in the full model were tested using the log link to provide coefficients interpretable as the ratio of net benefits, which can be termed 'relative net benefit'.[47] Huber White robust standard errors were added to address heteroskedasticity using the cluster option to account for the effect of complex survey design. A finite population correction was incorporated according to the number of episodes in the study area.

Continuous variables including household size and duration of diarrhea were checked to see if model fit could be improved with the use of spline terms. The importance of highly influential points was checked by calculating DFBETAs for fully interacted models, excluding caregivers with the top 10 DFBETA scores. Comparison of AIC / BIC scores indicated that omitting these points slightly improved model fit, although little difference was seen in the significance of the treatment variable. Since these extreme cases were considered important to the analysis to make results comparable to the CEA according to bootstrapping, reference case calculations were performed on the full dataset.

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[44] The influence of the skew in the cost component of the net benefit statistic is lower at lower levels of λ. Increasing λ often makes the distribution more normal as effects have more influence.

[45] 3,840 children had no cost and no episode, and 3608 had no cost alone, indicating an excess of zero values. However, a zero inflated model was not implemented to preserve the interpretation of cost-effectiveness of the intervention across the entire dataset.

[46] The Park test indicates chi-square values for Gaussian, Poisson, Gamma, and Inverse Gaussian distributions. Although p-values do not indicate a clear choice, the chi square statistic is lowest for the Gamma distribution.

[47] The ratio of net benefits is useful to provide evidence about whether the intervention is cost-effective, even if not represented on the monetary scale as with incremental net benefits.

7.2.8 Covariates tested

Covariates for the model were chosen according to an adapted form of the Andersen and Newman (1973) conceptual framework for treatment seeking (119), to be consistent with Chapter 6. A sensitivity analysis was performed testing the set of variables affected by the program.[48] To construct a wealth index for assessing the effect of assets on net benefit, principal components analysis according to standard methods (212, 219), using the component with the highest eigenvalue to construct a scale for classifying caregivers into quintiles. Descriptive statistics and regression analyses were performed in Stata 13, with program costing and generation of acceptability curves performed in Microsoft Excel.

7.3 Results

7.3.1 Power calculation

Given the available sample size, power calculations indicate that the study had over 95% power to detect a significant difference in incremental cost-effectiveness from λ if λ was below \$5.50 or above \$9.75 (Figure 11). Given our calculation for the reference case λ being \$14.80, this study was expected to have sufficient power to detect a meaningful difference in cost-effectiveness, and this result was robust to most sensitivity analyses (Tables 15 & 16).

7.3.2 Descriptive statistics and program costs

Comparison of covariates across study phases indicated that many of them were unevenly distributed (Table 18). Program costs are presented in Table 17. Expenditures on both capital and recurrent costs were higher in the public sector [managed by the NGO, Micronutrient Initiative (MI)], despite the fact that most people sought care through the private sector [managed by the NGO, Family Health International (FHI-360)]. This finding is explained by the fact that MI was responsible for the block, district, and state level review workshops to launch the program; for

[48] This set included knowledge of ORS and zinc, seeking treatment outside of the home (public facilities, public community based providers, and private providers), and being prescribed ORS and zinc

paying for its own personnel and travel expenses, and for the procurement of zinc and ORS (initially). Importantly, this costing did not include the salaries of health providers themselves, who were remunerated according to the status quo functioning of the health system. The most significant component of costs to FHI-360 were for subcontracts to other NGOs and West Coast pharmaceutical company, for training of pharmaceutical representatives in zinc and the SMS system to monitor sales, and managing of promotional booths called 'DAZT corners'.

Sample statistics for costs and health outcomes are presented in Table 19. Cost per average person in the sample decreased by $0.25, and diarrhea prevalence was reduced by 3.25%, leading to a dominant cost-effectiveness ratio not dependent on λ.

7.3.3 Regression outputs

In simple linear regression, the magnitude of the coefficients on the phase variable and their standard errors increased with higher values of λ except for in two specifications.[49] In simple linear regression, the coefficient on the phase variable was equal to the result when net benefit was calculated according to standard methods (-$0.25 compared to when λ = $0/episode averted). For all simple linear specifications tested, the intervention was dominant across values of λ in the unadjusted analysis (Table 20). These results were confirmed by the unadjusted CEAC, which shows that the intervention was cost-effective with 100% certainty for all values of λ tested (Figure 16). Results were robust to sensitivity analysis testing negative binomial and ordinary least squared specifications and the inclusion and exclusion of robust standard errors and adjustments for clustering (Table 20). Adjusting the model for the full set of covariates revealed a pattern of dominance according to study phase (Table 21, Figure 17). When interaction terms were added to the model, results remained cost-effective with over 95% certainty up to very high

[49] This trend held except for the simple generalized linear regression model with a log link, robust standard errors, and accounting for clustering; and the negative binomial model with the same adjustments

levels of λ, with declining levels of cost-effectiveness according to increasing levels of the ceiling ratio (Table 22). This finding indicates that the program is an inferior good, averting fewer episodes and costing less controlling for covariates for a small proportion of individuals (Table 22, Figure 18). This result was robust to sensitivity analysis using the set of covariates evaluated in the GEMS study (wealth index, child sex, education,[50] child age,[51] severity,[52] and duration of diarrhea) (Table 23) (95). Subgroup effects were observed with being given zinc showing reduced cost-effectiveness, and improved maternal education, being from a scheduled tribe, having knowledge about zinc, and diarrhea duration showing improved cost-effectiveness. No subgroup effects were seen for the specification using variables aligned with the GEMS study (95).

Diagnostic tests were conducted to check linear regression model assumptions. Variance inflation factors indicated that there was not collinearity between covariates. Breuch-Pagan / Cook Weisberg statistics confirmed that error terms around the regression line were highly heteroskedastic, with no signs of losing significance with ceiling ratios between extreme specifications of net-benefit with a λ = \$0 and λ = \$1,000,000. However, chi-squared statistics showed a declining trend, indicating that results were increasingly homoskedastic with the ceiling ratio. Omitting the top ten influential points identified through DFBETA made little difference to model outputs (Table 24). Testing results according to the set of parameters affected by the program revealed the same pattern of dominance seen in other model specifications.

7.4 Discussion

Net benefit regression provides a useful framework for evaluating the cost-effectiveness of the DAZT program, adjusting for imbalances in covariates. Results indicate that the program was dominant relative to conditions at the starting point of the survey before adjusting for covariates,

[50] I included both maternal education and paternal education with primary and secondary education cut-offs
[51] Despite the small range of child ages found in our dataset, age was included to be consistent with Rheingans et al (2012)
[52] I used blood in the stool as a proxy for severity to facilitate convergence

with unadjusted and adjusted estimates without interaction terms being comparable to those from a standard deterministic calculation. Adjusting for covariates and interaction terms did not have an important impact on conclusions, still recommending the program with 95% certainty.

Subgroup effects were observed, but should not be emphasized. Improved cost-effectiveness with each level of maternal education is not policy relevant as medical treatment should not be targeted according to socio-demographic characteristics (281). Little evidence was available in the literature on the impact of caste on amount of cost or diarrhea outcomes with which to pre-specify hypotheses. Being given zinc was associated with a reduced cost-effectiveness relative to not being given zinc as expected by the data structure as there was no reduction in episodes among children given zinc, although there was a reduction in episodes among children overall. Unadjusted costs among children that received zinc across the course of the program were reduced, but this trend disappeared in adjusted analysis with expected values actually showing an increase. Knowledge about zinc was consistent with the hypothesis that caregivers with knowledge would be able to spend more rationally, and represents a program attribute that may be targeted in further expansion of DAZT. However, targeting zinc by prescribers should not be done to promote rational prescription of antibiotics (278), and avoid costs associated with rationing medicine (67).

7.4.1 Policy relevance

Currently, only around 30 English language cost-effectiveness analyses evaluating interventions are available on PubMed in the Indian context indicating key gaps in the evidence base. Therefore results from this study are likely to be considered in an ad-hoc fashion by program managers and policy makers (282). In the near future, with the formation of a health technology assessment organization in India, results may be helpful to more systematic prioritization efforts (180).

The proliferation of large scale public health programs in the developing world, and the non-randomized nature of their data, provide increasing opportunities to conduct net-benefit regression when undertaking economic evaluation. In addition, this methodology is useful for randomized trials that fail to produce a balanced allocation of covariates.

7.4.2 Strengths and limitations

A natural limitation of the net-benefit statistic is the requirement to make an assumption about λ (86), for which definitions are only loosely defined (163), and are particularly unknown in the case of cost-effectiveness analysis in terms of natural units. However, this analysis provides a novel method for defining λ in terms of natural units using outputs from the LiST tool. A strength of the net-benefit framework is that it makes it unnecessary to quantify uncertainty around ICERs according to bootstrapping, which can be problematic due to the ambiguity of negative ICERs across quadrants (86).

The uncontrolled before and after study design limits the measurement of effectiveness. Imbalances between before and after phases were controlled for through the regression approach; however, no mathematical adjustment can control for unobserved characteristics in non-randomized study designs. In the case of this study, secular trends may have influenced results such as changes in living standards, source of water, and hygiene practices. In addition, the Hawthorne effect may have magnified effects (283). To some extent these effects may have been countered by secular trends in costs, which may have been expected to increase given current trends of economic development in Gujarat.

The fact that this analysis evaluates cost-effectiveness analysis defined in natural units limits capacity to compare results to cost-utility analyses of other interventions. However, outcomes measured in terms of natural units are often used in net-benefit regression (86, 109, 111), and outputs of this analysis are important in other ways. The finding that controlling for confounders and sets of those included did not have an important effect on cost-effectiveness strengthens the robustness of conclusions from calculations performed according to non-regression based methods.

7.4.3 Steps further

Statistically, non-parametric methods may be tested as a robust alternative to ordinary least squares to improve fit, in addition to the specifications tested in this analysis. The 'wild bootstrap' is appropriate given the heteroskedasticity in the residuals (284); however, goodness of fit tests and post estimation commands are not currently available in Stata.[53] A more flexible approach to modeling regression based cost-effectiveness analysis with separate equations for incremental costs and outcomes, linked together by their error term in seemingly unrelated regression (285).[54] This approach is useful for specifying models with different covariates for costs and outcomes, although makes several assumptions (286).[55] Alternative methods of accounting for clustering may also be tested, such as a two-stage non-parametric bootstrap or other methods (287).

7.5 Conclusions

This study evaluated the cost-effectiveness of the DAZT program to treat child diarrhea in Gujarat using a new formulation of the net-benefit statistic to accommodate calculation with 'health gap' measures. The main finding was that it is likely to be cost-effective according to a cost-effectiveness threshold derived from per capita GNI. This result is robust to the sets of covariates tested to adjust results, with unadjusted and adjusted results being dominant, and the

[53] It is necessary to write out manually the commands to perform the wild bootstrap itself, although Cameron and Trivedi provide the appropriate code which works for my data.
[54] Conditional mixed processes are an option for combinations of probit and linear regressions with correlated error terms
[55] Assumptions include that parameters are normally distributed, that there are constant variances between study phases, and that the correlation between costs and effects are the same in each study phase (Nixon and Thompson 2005).

fully interacted specification remaining cost-effective with 95% certainty. Recognizing the impossibility of controlling for unobserved factors, the program should be recommended for scale up given consistency with cost-effectiveness evidence from previous literature, and cost savings described in Paper 1. Methodologically, net-benefit regression is a valuable tool for evaluating non-randomized programs, and has promise as an analytic tool in the LMIC setting. Modifying the net-benefit statistic to accommodate 'health gap measures' has promise to make new specifications possible for net-benefit regression, such as GLM Gamma and negative binomial regression.

8. Paper 3

Cost-effectiveness of bundling diarrhea services in Gujarat India: A probabilistic analysis based on OneHealth and the Lives Saved Tool

Introduction: Bundling health interventions is a health systems strategy for exploiting synergies between interventions with joint inputs or complementary effects, and has been applied frequently in maternal and child health programs. The purpose of this study is to evaluate the cost-effectiveness of different bundles of interventions to prevent and treat diarrhea and pneumonia.

Methods: A league table was evaluated to define a bundle of services in the context of six districts of Gujarat, with component bundles defined according to service delivery channels. Coverage levels were defined according to conservative and universal scale up scenarios. Costs were calculated using an ingredients approach, with outcomes modeled using the Lives Saved Tool (LiST). Incremental cost-effectiveness ratios were calculated in 2013 US$ according to deaths and Disability Adjusted Life Years (DALYs) averted.

Results: The evidence base on the cost-effectiveness of interventions for pneumonia and diarrhea is currently incomplete in the Indian context. League table evaluation revealed that investment in health is strikingly low in Gujarat relative to what is recommended by cost-effectiveness evidence, with the current budget able to finance less than 8% coverage of zinc treatment for diarrhea. Calculations indicate that the full bundle of interventions is cost-effective, with a cost per DALY averted of $155.02 (95%CI: $128.58-$183.33) and $180.38 (95%CI: $149.86-$213.73) in the conservative and universal scenarios.

Discussion: Investment in the health system in Gujarat should be increased to scale up cost-effective interventions to prevent and treat child diarrhea and pneumonia. A pattern of expected synergies in adding further interventions to the bundle was not seen, although all bundles were well below a cost-effectiveness threshold of per capita GNI in Gujarat (US$1,653). Further cost-effectiveness analyses would strengthen the evidence base for rational policy making and health systems planning in the health system of Gujarat.

Key words: Diarrhea, Pneumonia, Cost-effectiveness, Zinc, Oral Rehydration Salts, India, Developing Countries, Packages, Bundling, Lives Saved Tool

8.1 Introduction

Bundling services is a health systems strategy in which several interventions are delivered at once to minimize costs to the patient and health system and maximize favorable health outcomes (288). Synergistic effects between treatment and prevention interventions can enhance benefits realized by the health system, and generate economies of scale that minimize joint production costs and reduce total costs. For example, health provider time per patient can be minimized, patient time in seeking care can be reduced, facility space can be utilized more efficiently, and medical records and administrative procedures can be standardized (118). Specialized resources can be used more efficiently by screening patients at lower levels of the health system and allowing treatment of conditions earlier in development when they are less expensive and more amenable to cure (288). Determining what interventions are essential for the bundle can be helpful from a health systems perspective, informing which should be provided by the public sector, and which should be left to the private sector or external assistance (288). The process of defining bundles can protect financing for cost-effective and equitable services from being diverted to services that are more intensely demanded such as hospital services (81). In addition, it can shift the mindset of policy makers from inputs to outputs, improving the effectiveness of the health system (81).

However, bundling also has potential drawbacks. A common concern among community health worker programs is the possibility of overburdening them with an excess of responsibilities (289), and the added need for prioritization within a recommended package can lead to inefficiencies (290). Bundles may be bundled out of logistical convenience, donor directives, organizational expertise, or specific lines of scientific inquiry, not lending to effectiveness and sustainability (83). In addition, the process of defining bundles of services can be used as a delaying tactic, with policy stagnating in discussion for long periods of time (81). The experience in Andhra Pradesh provides an example where bundling services was problematic – the bundle of services was defined by disengaged international representatives and academics (81), and a large amount of time elapsed between study completion and presentation of results (291), both hindering the implementation of the policy.

Bundling services in international health has roots in Alma Ata and the 1993 World Development Report (WDR) (288, 292). The latter defined an essential national package of cost-effective health services to which low and middle income countries could aspire to scale up coverage. This package focused on interventions that benefited poor people and addressed major sources of disease burden, and was designed through a league table approach (288). However, many approaches are available to defining service bundles. For example, UNICEF defined bundles of services for diarrhea based on a prevention and treatment classification (9). Bundling can also be done according to diseases that share diagnoses, medicines, and treatment protocols, such as diarrhea and pneumonia (239). Similarly, interventions can be bundled according to a risk factor that is amenable to intervention – although determining attributable risk by risk factor can be difficult (288). Bundling can be done by delivery channel, specifically by what one cadre of provider can reasonably offer. Interventions that target a particular patient group can be bundled together, such as neonatal care interventions (83, 89). Services can be bundled according to those that should be delivered through the public and private sectors respectively (288), or by economic sector (health versus other non-health sectors) (293-295). A final approach to bundling is according to which services can be delivered through the community versus facility levels of the health system.

There are many examples in public health where maternal and child health programs have combined interventions to provide packages of services. GOBI-FFF was an early package from UNICEF that included growth monitoring, oral rehydration therapy, breast feeding instead of early weaning or bottle feeding, immunization, family spacing, food supplements, and female education (296). More recent examples of bundling health services in LMICs include the expanded program on immunization (EPI) (297), and Integrated Management of Neonatal and Child Illness (IMNCI) (298). Integrating perinatal services delivered by Community Health Workers in Bangladesh, India, and Pakistan has proven to be feasible, resulting in significant reductions in neonatal and perinatal mortality (299-302). Bundling immunization and maternal and child health interventions (such as micronutrient supplementation or preventive malaria treatment (292)) has been found to increase coverage of child health interventions when interventions are carefully selected for compatibility and receive adequate support, but do not achieve levels of immunization coverage (303). A systematic literature review found insufficient evidence for improving efficiencies of resource use through bundling, and benefits were mostly not evaluated (304). The child health days strategy for delivering multiple interventions provides another example of bundling health services, and is particularly useful in areas where infrastructure is weak (116). The World Health Organization's CHOosing Interventions that are Cost-Effective (WHO-CHOICE) initiative evaluated bundles of child health interventions relevant to LMICs including: oral rehydration therapy, case management of pneumonia, supplementary food and nutrition counseling, vitamin A, zinc supplementation, vitamin A fortification, zinc fortification, and measles immunization (102).

Modeling studies make conflicting assumptions about whether bundling leads to efficiencies. Darmstadt et al emphasize the benefits of delivering services as bundles according to delivery channel (89). However, WHO-CHOICE found increasing incremental cost-effectiveness ratios as additional services were added to a bundle of child health interventions (102). The Lives Saved Tool (LiST) considers bundling efficiencies in terms of incremental time needed to provide services and in indirect costs. LiST has been used to evaluate diarrhea interventions from the UNICEF package of diarrhea interventions (9) for 68 priority countries according to conservative and universal coverage scenarios between 2011-2015. This study found additional costs of $0.80 per capita in 2015 for non-WASH interventions to achieve universal coverage, and found that the number of diarrhea deaths in these countries declined from 1.39 million in 2010 to 334,000 in 2015 (90).

The objective of this study is to evaluate the cost-effectiveness of bundles of interventions to prevent and treat diarrhea in six districts of Gujarat including Banas Kantha, Sabar Kantha, Patan, Surendranagar, Dohad, and Panch Mahals. Implementation was considered in the context of the the health system of India (Figure 19). This study draws on methods from Fisher-Walker et al (2011) (90), expanding the set of interventions to include those for pneumonia (239), consistent with those evaluated by Tam and Friberg in a recent UNICEF report (305). Re-analysis is relevant as the burden of disease estimates considered by Fischer Walker et al (2011) were too high at 1.4 million and 1.1 million deaths in 2010 and 2011 (subsequent studies have found 751,000 (114) and 700,000 (5) deaths for these years). In addition, Fischer-Walker et al (2011) did not calculate cost per death averted using the rationale that outcomes only include diarrheal deaths averted and do not account for the full impact, although only accounting for disease specific mortality is common in cost-effectiveness analysis (306-309). They did not translate deaths averted to DALYs averted, limiting comparison of results to the majority of cost-effectiveness literature in international health. Methods for determining coverage levels are not presented, and at-scale data are becoming available to inform more realistic targets for scaling up relevant interventions. Finally, only one previous project has used probabilistic sensitivity analysis (PSA) to evaluate uncertainty around estimates of the cost-effectiveness of multiple child interventions based on outcomes from the LiST tool (132). Our study uses a similar method to PSA, although models scaling up various sets of interventions through two hypothetical scenarios instead of evaluating an existing program.

8.2 Methods

8.2.1 Selection of interventions

Eleven diarrhea and pneumonia interventions were considered for each package including vitamin A supplementation, oral rehydration salts, therapeutic zinc supplementation, breastfeeding promotion, antibiotic treatment of dysentery, treatment of severe diarrhea, antibiotics for treatment and management of pneumonia, treatment of severe pneumonia, rotavirus vaccine, pneumococcal conjugate vaccine, and HiB vaccine. Prophylactic use of zinc was excluded based on the rationale that these programs will be difficult to introduce given the problems in implementing less intensive programs of zinc for diarrhea treatment, although efforts to promote these programs are recognized (125). Complementary feeding programs were excluded due to the lack of coverage data. While Water, Sanitation, and Hygiene (WASH) interventions are sometimes evaluated in cost-effectiveness analysis (140, 310, 311), they were excluded as Hutton et al (2004, 2007) argue that WASH interventions are better assessed by cost-benefit analysis (293-295) since they are not delivered through the health sector (WASH interventions are delivered by the Ministry of Drinking Water and Sanitation in India). In addition, Cairncross et al (2010) (312) emphasize the limitations of data parameterizing the effectiveness of WASH interventions and the need for caution when interpreting results from LiST (313). These interventions include improved water sources, water connection in the home, hand washing with soap, hygienic disposal of children's stools and improved sanitation – utilization of latrines or toilets.

8.2.2 Literature search

Each intervention was evaluated individually, a full package was tested (justified with a league table exercise), and interventions were tested according to delivery through a common service delivery channel (Table 25). The package of interventions tested in the league table was defined according to coverage levels that fit within the budget of the Gujarat Ministry of Health. PubMed, Scopus, Embase, and Google Scholar were searched for cost-effectiveness analyses evaluating interventions to address diarrhea and pneumonia in the Indian context using the search terms '[intervention name] cost-effectiveness'. Inclusion criteria were

1. Being from India, South Asia, or a LMIC, with priority given to articles identified from studies in that order.
2. Appropriate service delivery channel – for example, a mix of community and facility based channels for breastfeeding promotion is appropriate (4) instead of hospital based programs alone (314)
3. Presenting results in terms of incremental costs per death or DALY averted
4. Disaggregating costing data to facilitate calculation of the budget requirements

8.2.3 Decision making criteria

In addition to cost-effectiveness, other decision making criteria defined by Musgrove (1999) were considered (175). These included economic efficiency and ethical criteria.

Economic efficiency criteria

1. Whether the intervention is a public good
2. Whether positive or negative externalities are associated with the intervention
3. Whether the intervention can avert catastrophic health expenditures to households
4. Whether the intervention is cost-effective relative to the status quo, or a null comparator

Ethical criteria

5. Whether the intervention addresses diseases of poverty
6. Whether the intervention improves horizontal equity
7. Whether the intervention improves vertical equity
8. Whether the intervention saves lives ('rule of rescue')

8.2.4 Costing

Costs were calculated from a societal perspective consistent with textbook recommendations for economic evaluation (88, 133, 155). This calculation assumed a well-functioning health system, with adequate infrastructure and human resources, and that only the incremental costs of providing the additional services would be of interest to policy makers.

Program costs were drawn from a variety of sources due to the large number of interventions considered. Start-up costs consisted of training alone, assuming that no recruitment was necessary of new health workers. Levels of training included master training of trainers (1 event), training of supervisors in each of the six districts, and training of health workers. Lump sums were taken from the Haryana trial data [Lefevre et al, unpublished data], and scaled up to six districts. No international consultant or field testing costs were assumed due to lack of data, despite conventions to include them (224), and this may underestimate the true costs.

Facility costs consisted of those for administrative buildings, and were derived from DAZT program records assuming a headquarters in Delhi, and separate offices for public and private sector operations in Gujarat. Costs of health facilities were assumed to be the same across trial phases as no new building of facilities was anticipated, and facilities were not anticipated to remain open an additional number of hours. Expenditures on rent represented the value of facilities, which was also assumed to include the costs of utilities (electricity and gas, telephone and mobile phone, water) and maintenance.

Vehicle costs included one vehicle for the program supervisor and a vehicle for each of the program offices based on data from the Haryana trial [Lefevre et al, unpublished data]. No additional vehicles were assumed for health worker use, as it was assumed that these were provided by the existing health system. However, transport and storage was assumed for costs of the cold chain, for which costs were scaled to the population size of the six districts (315). It was assumed that distribution costs of medicines were included in their price.

In-service training of pharma partners in diarrhea epidemiology and benefits and use of zinc was based on DAZT program records. Additional training for each of the new vaccines was assumed to require seven modules lasting half of a day in total (316), with an additional half day on vitamin A administration. No additional training was assumed for breastfeeding counselling as ASHAs already provide this service. Also, it was assumed that health workers were already trained in providing antibiotics for dysentery and pneumonia, and in treating severe cases. No account was made for governance, management information systems, monitoring and evaluation, or overall health system strengthening.

8.2.5 Cost-effectiveness

Cost-effectiveness was calculated according to incremental cost-effectiveness ratios (ICERs), defined as the incremental cost divided by the incremental effects of each bundle of interventions (133). Both costs and effects were calculated according to coverage levels of the interventions in each bundle. Initial coverage levels were defined according to NFHS and Multi-Indicator Cluster Survey (MICS) data for rural areas (16), assumptions made by Fischer-Walker et al (2011) (90), and set to zero for vaccines considered as they have not yet been introduced. Conservative and universal coverage scenarios were modeled (90) according to a variety of criteria. Coverage levels for zinc and ORS were defined according to levels observed in the DAZT program between 2011-2013 (Chapter 6), and were assumed to follow linear trends to 2015. Increases in coverage of antibiotics for dysentery and pneumonia were assumed to occur proportionally. Vaccine and Vitamin A coverage levels achieved were defined according to existing levels of Diphtheria-Pertussis-Tetanus (DPT) vaccine coverage as they may be delivered together (16). Levels of breastfeeding were set according to values used in Fischer-Walker et al (2011) (90).

The number of severe diarrhea cases observed in each study phase was about 1%, consistent with OneHealth assumptions. While only half the number of severe diarrhea cases was seen at the end of the study as compared to the start, it was assumed that the program did not have a detrimental effect on treatment of severe cases, and that 100% were treated through the duration of the scale up.

The universal scale up scenario was defined using existing estimates from Fischer-Walker et al (2011) (90), which were based on expert opinion stemming from discussions between Christa Fischer-Walker and Nancy Binkin. Further assumptions were made for pneumonia interventions not covered in that paper. Coverage levels for the HiB vaccine were set at 96% in this scenario based on levels that were achieved in Bangladesh (14). Coverage levels for the pneumococcal vaccine were set to be the same as the HiB vaccine since they have the same dosing schedule (317), and no estimate was available from Fischer-Walker et al (2011) (90). Coverage of antibiotics for pneumonia was scaled up to 90% consistent with antibiotics for dysentery (90).

Outcomes were modeled using the Lives Saved Tool (LiST), which is a software program used to predict the impact of increases in intervention coverage achieved by large scale programs in terms of child lives saved (318). LiST is part of the Spectrum policy modeling system, which incorporates data from Demographic Health Surveys and Child Health Epidemiology Reference Group (CHERG) reviews of the effectiveness of interventions on disease specific mortality. Modules in Spectrum include demographic modeling, HIV modules, and the LiST tool. LiST calculates impact by attributing effectiveness to preventive interventions before curative interventions. Parameters were modified to reflect setting specific conditions such as demographic characteristics, initial coverage of interventions, and extent to which they were scaled up. However, as LiST is a deterministic model, effectiveness results were not given with ranges of uncertainty around them.

LiST projections were generated using established methods (318). The time frame was set according to the starting year of the DAZT trial (2011) extended to five years to be consistent with funding cycles (228), election cycles, and previous work (90). Conditions in India were described in terms of five categories of variables including maternal, neonatal, and child mortality including stillbirths; exposure to plasmodium falciparum, or zinc and vitamin A deficiency; risk factors for child illness; intervention coverage; and demographic data from the National Family Health Survey (318).

Resource requirements were drawn from the OneHealth manual, which is based on WHO clinical protocols. Costs were drawn from a variety of sources, outlined in Table 26. Personnel salaries and amount of time required were drawn from the LiST tool, which uses data from WHO-CHOICE (90). Costs of medicines were drawn from the Management Sciences for Health (MSH) International Drug Price Indicator Guide (319). Vaccine prices were taken from GAVI alliance sources (320, 321), and published literature (166, 167). Costs of materials were taken from the UNICEF supply catalogue (322), and other online vendors. Prices per intervention were multiplied by the population in need, or percent of the population that should be receiving the intervention annually (323). Resource requirements for each intervention are listed in Table 27.

Incremental cost-effectiveness ratios were converted to 2013 US$ using consumer price indices from the International Monetary Fund for national level estimates, or percent change in average consumer prices for regional level estimates (229). Currency conversion for one study was performed using the mid-year exchange rate from OANDA.com (324). International dollars were converted to United States dollars using a purchasing power parity index from the World Databank (14). Uncertainty around ICERs was quantified using non-parametric bootstrapping (133), with simulations generated with Monte Carlo Simulation using a visual basic macro for

Microsoft Excel. Beta distributions represented probabilities given that they are bounded by zero and one, and gamma distributions represented costs given that they are bounded by zero and have a positive skew (139). Alpha and beta parameters for these distributions were defined using the 'method of moments' according to the mean and variance of a triangular distribution, defined by the best estimate, low, and high values drawn from the literature (325). Calculation of costs and probabilistic sensitivity analyses were performed in Excel using a Visual Basic for Applications macro.

8.3 Results

8.3.1 League table results

For the league table exercise, the literature search revealed 19 studies with ICERs eligible for consideration, although most were excluded from analysis. Two studies on vitamin A fortified mustard and rice were excluded as outcomes were not assessed with respect to diarrhea (326, 327). Dabral (2009) evaluating measles vaccines was excluded as measles deaths due to diarrhea are classified as measles by international conventions (90). An analysis of ORS and recommended home fluids by Islam et al (1994) was excluded due to its date (328). Gupta et al (2013) was excluded as it was conducted for a Haryana state perspective (329), and Gujarat specific data was available from Clark et al (2013) (166). Other studies excluded are listed in Table 28.

Disaggregated cost data was available for five studies which could be included, listed in Table 29. If a ceiling ratio of per capita Gross National Income for Gujarat is used (US$1,653), the necessary budget would be $47,283,301 to finance all five interventions listed at full coverage. However, given that the total public and private expenditures for health in Gujarat was $1,261,866 in 2008-9 (330), and with 18.1% of people living in the study districts, the budget would be $228,538 if allocated proportional to population. Within this budget, only zinc supplementation could be financed, and at less than 8% coverage.

8.3.2 Other criteria

Other diarrhea interventions were considered for inclusion, but there was reason to omit them from the league table, as indicated in Table 28. Therefore, the set of interventions evaluated with CEA was incomplete, limiting the scope of the league table. However the case was made to include these interventions in the recommended package based on the following rationale according to Musgrove (1999) criteria (175).

Both herd immunity and interventions that lower disease incidence are public goods as their benefits are spread across the entire community whether or not individuals choose to consume them (331). Unvaccinated individuals enjoy the benefits of immunity despite not choosing to receive the vaccine. In addition, breastfeeding reduces incidence of both diarrhea and pneumonia (5, 332). These goods are non-excludable and non-rivalrous (333) in that individuals cannot be excluded from use, and consumption by one person does not preclude consumption by another. Since all of the other interventions in the league table reduce incidence, they all can be considered public goods.

Many externalities, or costs and benefits beyond the scope of the analysis, are associated with these interventions. Breast milk diminishes the adverse effects of diarrhea on nutritional status (4), contains many immunobiological components which confer protection to diseases beyond just pneumonia and diarrhea (332), confers protection against post-partum depression (334), and helps mothers provide adequate space between births (335). Vaccines, as discussed, confer herd immunity, which protects unvaccinated people from illness (167). Zinc confers protection beyond diarrhea and pneumonia treatment and prevention, including general benefits to the immune system (336), and contribution to child growth. From a health systems perspective, scaling up zinc can increase uptake of ORS (337). Both zinc and vaccines can slow the development of antimicrobial resistance in affected organisms by reducing the amount of antibiotics prescribed for bacterial infections (4, 338, 339). Vitamin A provides protection against night blindness and xerophthalmia (340). Antibiotics can treat subclinical infections, although their overuse can lead to unintended negative consequences such as drug resistant strains of bacteria. At a macro level, control of diarrhea and pneumonia has external benefits to other sectors, such as transportation, tourism, and manufacturing (338).

Hospitalization for both diarrhea and pneumonia can have serious financial implications to caregivers. Alamgir et al (2010) showed that hospitalization for pneumonia can become catastrophic for poor families in Bangladesh (341). While Sheih et al (2013) conclude that diarrhea hospitalization was unlikely to cause catastrophic expenditure in Ho Chi Minh city (342), Rheingans et al (2012) highlight the importance of rare, expensive events (95).

Despite being common enough to affect everyone – rich and poor, old and young, and people in developed and LMICs – diarrhea particularly affects people living in poverty due to its association with unhygienic environments (4). In addition, the incidence of pneumonia disproportionately affects the poor (305, 332, 343). Breastfeeding has the potential to reduce inequalities in health (344) and is possibly progressive – mothers in the richest wealth quintile were less likely to exclusively breastfeed in India (345) and Pakistan (346). With diarrhea affecting the poor preferentially, mothers of the highest priority are doing more breastfeeding. Treatment with zinc, however, is regressive, with DAZT data showing caregivers in the least poor quintile being nearly twice as likely as giving zinc as those in the poorest two quintiles [Lefevre et al, unpublished data]. The distribution of vaccination across wealth quintiles improved between the first and second rounds of the National Family Health Surveys in urban areas, but not in rural areas (347). Antibiotics are widely prescribed, even in rural areas, which has the semblance of equity but poses the risk of antibiotic resistance (348).

All of these interventions prevent or treat diarrhea or pneumonia, the two leading causes of child death worldwide (5), which gives the semblance of addressing the 'rule of rescue'. However, 'rule of rescue' refers to interventions that can be visibly observed to save an identifiable life (349). As the interventions considered for the full bundle address treatment of non-severe cases, or are preventive measures, they do not satisfy the 'rule of rescue'.

8.3.3 Cost and cost-effectiveness results

Figure 20 shows the number of lives that can be expected to be saved each year with implementation of the full package of interventions according to the coverage levels used in the study (Table 30). Number of child deaths declined from 7,503 in 2011 to 4,749 in 2015 in the conservative coverage scenario, and from the same initial number to 3,499 in the universal coverage scenario. The total recurrent cost over five years was \$48.3-\$62.9 million, with the largest component being for oral rehydration salts due to the frequency of episodes and high coverage, and the smallest component being antibiotics for dysentery (Table 31). Program costs totaled \$640,899 per year (Table 32). Assuming that program costs were distributed evenly across interventions, the most cost-effective intervention was breastfeeding promotion due to its low cost, which became cost-saving when discounted at 3%. The least cost-effective (Table 33) was zinc supplementation due to the high frequency of episodes, low number of deaths averted relative to ORS (66% lower), and high costs (33% higher). For treatment of severe diarrhea and pneumonia, cost-effectiveness was undefined as it was assumed that the program did not have an incremental effect on health outcomes.

For the total package, incremental cost effectiveness ratios were found of $159.85 (95%CI: $134.86-$192.27) per DALY (3,0) averted in the conservative coverage scenario, and $185.50 (95%CI: $156.65-$221.80) per DALY (3,0) averted in the universal coverage scenario (Table 34). Considering a 3 dose regimen of rotavirus vaccine did not have an important effect on results, raising the cost-effectiveness of the package in the conservative scenario to $159.85 (95% CI: $134.86-$192.27).[56] Results were sensitive to alternative DALY scenarios using variations in the discount rate between 0% and 6%, although were robust to formulations with and without age weighting. By delivery channel, cost varied according to comprehensiveness of the package (Table 35), and cost-effectiveness ranged from $95.49/DALY (3,0) averted (95%CI $75.99-$117.72) for community based interventions to $208.53/DALY (3,0) averted (95%CI $196.87-$233.49) for the outreach package in the conservative scale up scenario (Table 36). Differences in cost-effectiveness between scenarios were significant for the outreach and clinic bundles.

8.4 Discussion

Results from this study emphasize the cost-effectiveness of community based care relative to facility based services. However, which package is optimal for implementation will depend on the setting (292), including factors such as infrastructure, geography, cultural barriers, utilization patterns, financing systems, and budgets. In each context, the process of designing or adapting a package will allow health systems to use a degree of rationality in decisions made about what interventions are given the highest priority. This process will facilitate health systems planning in terms of coordination with manufacturers, purchasing, and training of human resources. However, assumptions of the process should be recognized, including that the system operates with technical efficiency, referral systems are well-functioning, vehicles and equipment are in good condition, sufficient staff exist where they are necessary, drugs are available, and facilities are open (288).

[56] The cost effectiveness of the rotavirus vaccine individually increased from $147.16 to $201.44 in the conservative scenario.

One of the main messages from the league table exercise is that there is a lack of cost-effectiveness evaluation of key interventions to address diarrhea in the Indian context. More work should be done to evaluate complementary feeding, antibiotics for dysentery, and vitamin A supplementation with a focus on diarrhea to fill gaps in the evidence base and shift attention away from interventions sometimes seen as 'magic bullets' such as vaccines (166-168). These studies are expected to be of increased relevance with the formation of a health technology assessment organization in India to guide decision making in the public sector, which is expected to increase in importance in the Indian health system (180).

The literature based league table that resulted from this analysis suggests that all interventions should be adopted in Gujarat based on cost-effectiveness evidence alone from an aspirational perspective (81) using per capita Gross National Income (US$1,653) to define cost-effectiveness (Table 29). The total budget necessary to introduce these interventions in the six DAZT districts is $43 million, indicating that budgets for health care must be dramatically increased or reallocated to address the disease burden in ways that are cost-effective, anticipating the rapidly growing population. This process can be difficult due to the inertia of historical factors (spending patterns, distribution of infrastructure, skill mix of healthcare providers and their locations, socioeconomics of the country, and demographic and geographic factors), political pressures and ideologies, and administrative procedures as allocation of government budgets not usually organized by type of intervention (although donor investment sometimes funds programs this way) (154, 288). In the case of diarrhea interventions, balance must be found between allocation to the Ministry of Health and Ministry of Drinking Water and Sanitation, professional organizations, manufacturers, government sponsored insurance schemes for the poor (Rashtriya Swasthya Bima Yojna), and other governmental and non-governmental organizations – particularly if WASH interventions are to be compared to those delivered by the health sector.

Budgets may also be organized according to input categories including personnel, supplies, maintenance, training, transport and other factors.

Zinc is the least cost-effective intervention in the league table based on our model, but is the most cost-effective in the league table based on published literature. This discrepancy stems in part from the fact that zinc was evaluated alongside ORS in the Haryana study [Lefevre et al, unpublished data], but these interventions are evaluated separately in our model. When evaluated together, fewer DALYs were averted, although the joint cost-effectiveness was more favorable than the cost-effectiveness of the interventions evaluated individually due to synergies in staff time and treatment seeking costs. From a programmatic perspective, it can be argued that programs to scale up zinc can stimulate progress in scaling up ORS coverage (337), which is the intervention that averts the most DALYs due to diarrhea (Table 33).

Breastfeeding counselling is also noteworthy as results between the league table approach and cost-effectiveness calculation are discrepant. In the literature based league table, breastfeeding promotion is the least cost-effective intervention, although our study argues that it is the most cost-effective, with low budgetary requirements relative to other considered interventions (discounted at 3%, the program would have negative incremental costs in the conservative scenario due to modest levels of expected scale up). The age specific evidence base for the LiST tool for averting mortality was different (350, 351) from the estimates used in the DCP2: 10.5% (range 4%-17%) (4). In addition, breastfeeding has many externalities, benefits the poor, and is equitable. Our study found that breastfeeding promotion is the most cost-effective intervention evaluated due to its potential to save 67-578 lives at a negative or low incremental cost to society.

Increases in funding alone will not have an impact if health system capacity does not exist to respond to the new incentives. The level of infrastructure in the six districts of the study area is comparable to other districts in Gujarat (Table 37); however, also comparable is the fact that only 78%-92% of positions in the public health sector are filled (352). Health care in rural India often suffers from high levels of absenteeism, callous attitudes of providers, shortages of medicines, and inadequate supervision and monitoring (353). Low levels of managerial capacity and lack of demand due to low quality services pose additional challenges to absorptive capacity (354). There is some evidence that rural providers have had success in using increased investment to stimulate demand for family planning and vertical programs such as polio vaccination, however, scaling up absorptive capacity for channeling money to provide other services is a health systems challenge that requires long run solutions (355).

As can be indicated through this analysis, decision makers face the choice between expanding the number of interventions included in packages, or extending coverage to new geographic regions and non-poor parts of the population. Literature indicates that as less accessible populations are targeted, increasing coverage may raise marginal costs above average costs (288, 292). However, an important finding from this study is that increasing coverage did not significantly worsen cost-effectiveness, despite arguments that reaching populations located remotely from urban centers is more costly for less return in terms of health. The pattern associated with increasing the number of services in the package is less clear, although it has the risk of reducing equity in the delivery of services (292). Children in LMICs have been cited as an example of inequitable distribution of health services as most rich children have access to several life-saving interventions at the same time, where poor children may have access to 1 in 10 (292). An alternative is for financing bodies to pay for certain inputs, and let the healthcare providers determine what services will be provided (81) – but this approach often leads to delivery of services of questionable value (288).

8.4.1 Engaging the private sector

Delivery of the interventions discussed was balanced between the public and private sectors, although conceivably, the program could have been conducted exclusively through the private sector. This assertion can be supported by health financing patterns in India – 80% of health care is financed privately in India, and 80% of private spending is through out of pocket payments (67). Specific considerations for league table analysis within the context of the private system are that it is less relevant whether the intervention is a public good, and the budget constraint should be defined to include more than just the health sector budget (adding out of pocket and insurance expenditures). Upon implementation, the government can engage the private sector through reimbursement mechanisms, best practice formularies, drug pricing guidelines, contracts with non-governmental organizations, monitoring mechanisms, and the requirement that insurance schemes and private providers provide a minimum number of interventions included in the package (180, 288).

Vitamin A supplementation has been promoted through the private sector using social marketing (356), although the public sector has substantial control over Vitamin A programs (357). ORS may be more effectively provided through the public sector as evidence suggests that for-profit providers are 15% less likely to provide ORT than public providers, corroborated by several studies from the 1980s and 90s (358). Pharmacies are privately owned and are less likely to provide ORS than other facility types. There is no evidence about whether breastfeeding promotion is more effectively provided through the public and private sector, although advice could be delivered by both.

Vaccines may be more effectively delivered through the private sector as the cold chain is better maintained than in the public sector (359). Private sector manufacturers in India are the major supplier of vaccines to UNICEF, and a large number of them are administered through the private sector in India (360). However, vaccine deployment is also part of the National Rural Health Mission (360), which is public and subsumes the Universal Immunization Program (UIP). The central government makes all of the decisions about vaccine introduction, and is responsible for procuring all of the vaccines in the country. State governments in India execute vaccine programs (360).

Antibiotics for dysentery and pneumonia can be delivered through both sectors, although might be prescribed more rationally through the public sector. 80% of antibiotics that were prescribed in DAZT were by private providers, but there is no indication about what percentage of this was for dysentery. Pediatricians in New Delhi working in the private sector were more than twice as likely to prescribe antibiotics for diarrhea as those working in the public sector (361). The problem with rational use of antibiotics in the public sector is drug availability. In Delhi, the private sector had better availability of more expensive and popular antibiotics, where the public sector had problems maintaining availability of essential antibiotics (362).

8.4.2 Strengths and limitations

There are several strengths to this analysis. It has a setting-specific scope, which will be useful to policy makers in Gujarat. Translating deaths averted to DALYs averted makes results more comparable to other studies using the same metric, such as those evaluated through WHO-CHOICE and the Disease Control Priorities Project (162, 363). Bundling diarrhea and pneumonia interventions together reflects current thinking of the Global Action Plan for Pneumonia and Diarrhea (GAPPD) (239), increasing its relevance to policy, and updating methods from previous work (90). Generating outcomes with LiST gives comprehensive consideration of the available data from large surveys for health outcomes, and incorporates attribution of lives saved to specific interventions in a rational way.

There are also several limitations to this analysis. The league table exercise is not based on a systematic review, and important studies may have been missed. Among those studies found, the full range of interventions was not represented, making a comprehensive consideration of cost-effectiveness according to thresholds impossible. While it is possible to quantify the relative importance of cost-effectiveness to other decision making criteria with appropriate data collection and methods (282), no attempt was made at multi-criteria decision analysis in our study. Methodological heterogeneity affected the sample of studies used in this analysis, and it was difficult to assess some attributes due to lack of reporting. For example, the perspectives of the analyses were a mixture of the public sector (125, 166), societal (70, 167, 168), or not stated (4) – reflective of reviews of the cost-effectiveness literature (364). This inconsistency mainly affects cost, which is the element most likely to vary across settings (365). Only one study gave perspectives on generalizability (70), although most analyses included were already done from a national (166, 167) regional (4, 125), or multicountry (168) perspective. Only one study presented ranges of uncertainty around ICER estimates (70), which has been argued to be essential in league table methodology (366).

There was inadequate reporting of what comparison strategy was used in included studies (4, 125, 167), and studies were mixed between those using comparators representing a null scenario (no intervention) (166, 168) or status quo conditions (70). Contrary to the assumptions of generalized cost-effectiveness analysis (227), Drummond argues that even with no intervention in the comparison arm (e.g. a no-screening scenario), some costs and benefits are inevitable due to passive case detection or other mechanisms, and that these outcomes should be accounted for in analysis (366). Even in very poor health systems, some degree of health seeking behavior can be expected in the absence of a program, although under the assumption that the treatment is available in the market.

The discount rate has become standardized at 3% in the international health literature, consistent with WHO-CHOICE (88) and DCP2 guidelines (130), and was either 3% (70, 166-168) or not stated (4, 125) in our selection of studies. An advantage of economic evaluation in the international health context is that DALY weights are provided by the WHO (231), reducing the amount of heterogeneity in utility weights that affects the high income country literature (366), although the new edition of the GBD study has released disability weights to revise those based on expert opinions that it provided in the past – improving the empirical foundation of the evidence base (138).

In calculated cost-effectiveness estimates, this analysis does not account for the fact that different children will have access to different sets of interventions – some will have access to many interventions, others will have access to few – affecting the effectiveness of interventions. Health systems strengthening costs were excluded from the analysis, which can be substantial and necessary to achieve technical efficiency. Data for program costs was patchy, and drawn from a variety of sources, although this limitation is typical of modeling exercises evaluating outcomes not prospectively planned before data collection (for example the World Health Report 2000 relied on synthesized and imputed data (367)). Cost curves and coverage scale up trajectories may be non-linear, such as the sigmoidal trajectories for scaling up child health interventions assumed by the WHO (368), although it is not clear what precise shape to give these curves given the available data. While ranges of effect sizes for the respective interventions are available in the CHERG reviews informing the LiST tool (34, 50, 369-376), it is not clear how some of them align with the reference case chosen for the model (313), restricting these parameters from being included in the probabilistic sensitivity analysis. Evaluating interventions in isolation is artificial, and the modeling techniques used only account for sequential attribution of lives saved and some synergies in costs in terms of incremental amounts of time spent delivering interventions.

There are limitations in how recommendations of packages of services may be implemented. No consideration is given to the tradeoff between coverage and quality – whether expanding number of health workers includes those of lower competencies, or whether programs functioning under tight deadlines can avoid taking shortcuts that affect effectiveness (292). Alternative delivery strategies are not considered, or their effect on costs or effectiveness, although their cost-effectiveness should be considered along with that of the interventions themselves (292). A constraints analysis could be done to assess these and other barriers to scaling up.

8.4.3 Further research

The model should be further developed to account for synergies between the costs of each intervention, and to better reflect the realities of the health system in Gujarat. Consultation with health officials in Gujarat is needed to determine the face validity of results, fill missing program cost components, and better define assumptions. The emergence of the new Rotavac vaccine in India (377), and the controversy surrounding its approval for the Universal Immunization Program (378), indicate that it should be studied once estimates exist on its impact on mortality. As the costing component of the LiST tool develops, parameterization can be selected according to the translog functions that it uses to generate costs. Further development to make the LiST tool probabilistic could be done on its underlying spreadsheets using the VBA macro used in this chapter.

8.5 Conclusions

This study evaluated the cost-effectiveness of scaling up zinc and other interventions to prevent and treat diarrhea and pneumonia in the context of rural Gujarat India, using outcomes predicted by the LiST tool. The analytic approach is new to this area in that it uses probabilistic sensitivity analysis to evaluate uncertainty around ICERs. The main finding is that investing in diarrhea and pneumonia interventions is highly attractive in the six districts of Guajrat included in the DAZT program, although increases in investment and health systems strengthening are necessary to ensure adequate coverage and realize the full benefit. A clear pattern of efficiencies in bundling increasing numbers of interventions was not seen in this analysis, although may be revealed with more sophisticated modeling and operational research. In addition, inefficiencies in expanding services to greater proportions of people may not be inevitable, with further costs balanced by further health gains.

9. Policy implications

9.1 Introduction

This main objective of this dissertation was to evaluate the economic case for the DAZT program in rural Gujarat India, and theoretical argument for investment in the context of other diarrhea and pneumonia interventions. Paper 1 evaluated the costs to caregivers of providing diarrhea treatment to children under 5, changes in these costs over the course of the DAZT program, and factors associated with costs. Paper 2 evaluated the cost-effectiveness of the DAZT program and the importance of controlling for covariates given the uncontrolled non-randomized study design of the program evaluation. Paper 3 examined the cost-effectiveness of the DAZT program when bundled with other interventions to prevent and treat diarrhea and pneumonia, and compared modeled cost-effectiveness estimates of these interventions with results found in the literature and current health expenditures in Gujarat. Main themes are summarized in Figure 21. The goal of this research is to inform investment decisions that will increase the effectiveness of the health system in rural Gujarat given limited resources. Given that the health system in this area is largely private, this research is expected to inform decisions faced by formulary developers, clinical practice guideline developers, and social franchises deciding which services to provide – in addition to a benefits package provided by the public health system.

9.2 Summary of chapters

The analysis in Paper 1 showed that costs to caregivers were reduced in the two years of the program. The main drivers of costs were wages lost, purchase of other drugs such as antibiotics and antidiarrheal medicines, and transportation costs. Unadjusted analysis indicates that the biggest decline in costs was among private providers, although these providers remained the most expensive sources of care. Costs were lowest at community based public providers (ASHAs and AWWs). The program was not associated with a change in the odds of incurring a cost, but was associated with a lower overall economic cost to caregivers across the course of the study controlling for confounders. Per million population, the program was associated with a cost savings to society of $687,572. In future development and in scaling up to other areas, the program should focus on service delivery through private providers, where most care was sought, and develop strategies for encouraging increased use of public community health workers. These findings emphasize the importance of the health systems component of the intervention as giving zinc was not associated with lowering the cost of treatment to caregivers controlling for other covariates.

In paper 2, the cost-effectiveness of the program was evaluated using a net benefit regression framework building on methods of Hoch et al (2002) (86). A novel adjustment to these methods is introduced in reformulating the net-benefit statistic to accommodate health gap measures, which opens the scope of net-benefit regression to new econometric modeling techniques. Unadjusted analysis indicated that the program was associated with fewer episodes and lower costs to the health system from a societal perspective, and adjusting for covariates did not alter the recommendation in favor of the program. Costs to caregivers were the main driver of costs, which were reduced by over half across the span of the program, and exceeded program costs by an order of magnitude at study completion. More work is necessary to determine why the prevalence of diarrhea was reduced as it could have been due to secular trends unrelated to the program such as improvements in living conditions, access to safe water, and sanitation practices; or due to other factors such as the Hawthorne effect or regression to the mean.

In paper 3, the review of studies evaluating interventions for diarrhea and pneumonia revealed that all are cost-effective, although public and private expenditures are currently insufficient to provide them at any reasonable level of coverage. The set of interventions evaluated in the literature is incomplete, and further work is necessary to evaluate complementary feeding, antibiotics for dysentery, vitamin A supplementation, and antibiotics for treating and managing pneumonia. The case can be made for all interventions considered using criteria from Musgrove (1999) (175), although some degree of prioritization is expected to be inevitable given current budgets and health system capacity.

Modelled results from paper 3 indicate that incremental costs of scaling up the full package of services are expected to be between $12-$20 million in the study area, and are expected to avert 2,754-4,004 deaths. Calculations suggest that the total package was highly cost-effective at $155.02 (95%CI: $128.58-$183.33) per DALY averted in the conservative scenario, which is well below the per capita GNI in Gujarat of US$1,653. The most expensive and least cost-effective intervention was zinc supplementation due to the frequency of episodes, its higher per unit cost, and modest DALY reduction relative to ORS. The least expensive and most cost-effective intervention was breastfeeding promotion due to its low incremental cost, which was negative in the conservative scenario with a 3% discount rate. Cost-effectiveness of any intervention or bundle of interventions never exceeded the per capita GNI threshold. The main message from this analysis is that health sector budgets should be increased, ensuring that absorptive capacity exists to deliver the services, and that diarrhea and pneumonia interventions are a good investment.

9.3 Policy and implementation context

Basing decisions about what interventions to provide through the health sector on cost-effectiveness is consistent with objectives of making both national and donor investment more efficient. International aid and avertable disease burden are not well aligned in many cases, with the exception of some multilateral donors such as the Global Fund and GAVI, and some bilateral agreements between the UK, Germany, Denmark, and recipient countries (154). Child health interventions are some of the most cost-effective available to low- and middle-income country health systems (102, 379), and saving child lives is consistent with Millennium Development Goal 4, which is due to be replaced by Focus Area 3 of the Sustainable Development Goals (380). Making services available close to client minimizes travel expenses and time lost from paid employment, which is consistent with Alma-Ata article VI to make services universally available to individuals and communities at a cost that they can afford (381). Given these mandates, it matters how diarrhea programs are promoted to policy makers. Based on an analysis using Policy Maker software (similar to stakeholder analysis), Bump et al (2012) advocate promoting diarrhea programs as part of a technology and vaccine implementation strategy, or as part of a health systems strengthening strategy (92).[57]

From a national level policy perspective, zinc and ORS are already advocated by the Indian government for the treatment of child diarrhea (42); however, scale up has been slow given the policy constraints and supply and demand side challenges mentioned in the introduction that have inhibited widespread coverage. To address these obstacles, DAZT partners have committed $1.5 million to support the state government in training 97,000 health workers in the proper use of zinc and ORS to scale up coverage to all 26 districts of Gujarat (382) and further areas of Uttar Pradesh (383). This policy is consistent with the constitution, which recognizes the importance of serving marginalized groups.

Whether scaling up zinc coverage nationally is feasible depends on manufacturing capacity, which currently includes a limited number of national and international companies (61). The most notable is Bharat Immunologicals and Biologicals Corporation Limited (BIBCOL), which is a government owned corporation with the capacity to produce 240 million tablets of 20mg scored tablets of zinc sulfate per year (59). At least five other companies (brands) exist in India,

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[57] Bump et al (2012) acknowledge that promoting diarrhea programs as a child health strategy is more feasible now than it was in 2008, when support for child health programs had waned.

including Zuventus (Zinconia), Dr Reddy's (Z and D), Wallace (ZN), USV (Trustim), and Emcure (Emzinc) (61). Sales in India have increased dramatically since 2005 (61), with some companies selling exports. In addition, Gitanjali and Weerasuriya argue that production capacity to address the burden of diarrhea in India appears to exist (56).

Feasibility also depends on the presence of infrastructure and human resource availability and receptiveness to decision making based on cost-effectiveness evidence. There are more private doctors and community health workers than other cadres of health worker in Gujarat (352), with the National Rural Health mission aiming to establish 400,000 ASHAs (384) that can provide close to client care for the frequent occurrence of episodes. Having the appropriate skill mix of cadres in each geographic area is important to ensure widespread coverage of zinc and ORS, coupled with appropriate referral and management of severe cases.

Economic evaluation has been criticized as politicians tend to approve interventions that affect themselves and their own families, and generally do not like to acknowledge explicit rationing as it is always associated with a bad outcome for some group, incurring costs to decision makers who do not stand to benefit from the decision (385). In addition, policy makers may not understand methods and jargon, and study results may not always be produced in a timely manner (385). There are identifiable methodological problems in many evaluations, and results from studies are not always transferrable to the relevant jurisdiction (385). In defense of economic evaluation, it offers a useful means to structure thoughts about both costs and benefits, and is rarely considered as a sole decision making criterion (175, 385, 386). Priority setting is particularly important in emerging markets where budgets are limited (154), and to identify new priorities as these countries progress through the demographic transition, experience economic growth, and confront a 'triple burden of disease' (10, 11).

9.4 Amount of investment recommended

Results from this dissertation promote the continued scaling up of zinc to similar areas with a high burden of diarrhea and limited access to appropriate treatment. Diarrhea treatment costs caregivers $7.6 million in the six survey districts per year, and $1.5 billion scaled up to the country level.[58] Results from these analyses indicate that zinc is expected to save caregivers money and be cost effective with >95% certainty controlling for other factors. Based on program cost data, the amount of investment recommended by this analysis would be $88,328,946 nationwide. With universal coverage, this investment could be expected to provide caregivers with an savings of an order of magnitude at $818,916,895 (387). Politicians might justify this investment with projections with how the resulting savings might boost economic development, and devise strategies for channeling some of the savings into tax revenues so that the program pays for itself.

9.5 Importance of close to client services

The most favorable cost of service provision through ASHAs and AWWs emphasizes the importance of community based delivery. The case has been made that CHW programs are cost-effective health systems strategies that reach underserved populations with effective, low-cost interventions (388). However, evidence on the cost and cost-effectiveness of CHW programs is only recently emerging to make informed discussion of the economic case for these programs possible (89, 274, 389-392). Our study makes the case for the DAZT program in terms of cost, although it was not possible to evaluate the relative cost-effectiveness of different service providers since observed outcomes were the same across all of them.

[58] This calculation assumes costs from the endpoint survey for the six study districts, and initial survey costs for the national estimate since it is assumed that similar programs to DAZT do not exist in most areas of India.

Health systems may be able to support scaling up the DAZT program to other areas with emphasis on close to client providers. A 2011 report indicates that only 10% of sanctioned ASHA positions were vacant in the study area, which is comparable to other districts in Gujarat (352). However, there is a shortfall of 12% of the required 7274 auxiliary nurse midwives (ANMs) at subcenters in Gujarat, and a shortfall of 23% of the required 8432 ANMs at PHCs (393). National trends for scaling up CHW numbers are encouraging, with an increase in female health workers of 56% between 2005-2012 (394), changes in policy to post two female health workers at each subcenter, and the commitment of the National Rural Health Mission (NRHM) to provide human resources in underserved areas (395). However, producing more CHWs cannot be expected to automatically scale up appropriate diarrhea treatment. Historically, community health worker programs in India have suffered from various problems, such as conflicts about remuneration, ill-defined definitions of responsibilities, and lack of community ownership; although these issues are being addressed in current CHW programs (396). In addition, knowledge retention among health workers needs assessment before they are allowed to work in the field, as well as refresher training (397). Further challenges to scaling up services to new areas include absorptive capacity, management constraints, lack of regulation, and absenteeism (354). An alternative strategy is to increase the work hours and responsibilities of existing ASHAs as they currently only work 25 hours per week (397).

3.1 Bundled services

This study also indicates that bundling can be an attractive health systems strategy for scaling up priority services efficiently. Several countries have attempted provision of bundled services, particularly through the Minimum Care Packages, although with mixed results (290, 398, 399). These findings emphasize that the method that services should be bundled depends on the financing capacity, drug supply, human resources, working conditions, and the health systems structure of the area. Conversely, Salam (2009) discusses implementation of services with greatest impact (400), implying that health systems should adapt to fit recommendations based on the published literature. Whether a normative view or consideration of existing conditions is taken, the bundling framework is useful to consider decisions in a framework more representative of how interventions will be implemented, rather than the individual context in which interventions are usually evaluated in cost-effectiveness analysis.

3.2 Gender bias

Gender bias is a commonly recognized problem in India, which ranks 101 out of 134 nations worldwide in level of gender equity in health and survival (401).[59] However, the lack of evidence of an influence of child sex on costs and cost-effectiveness in our analysis is notable. In literature, there was an absence of evidence of inequality for care seeking in the more developed state of Kerala (193), although an absence of evidence is not evidence of absence in scientific analysis. A contingent valuation study in Chennai indicated that parents were willing to pay more for diarrhea treatment for a male child than for a female child when adjusted for duration and severity of the illness, particularly among more educated households (189, 192). NFHS-III data showed evidence of gender bias in diarrhea care seeking nationwide in 2005/6 (191), and gender bias has been found in other child health indicators (402). Gujarat is already a state where gender bias in child health is a recognized problem (402), and the problem may worsen as the state develops and people become more educated. However, rewards for 'whistle-blowers' on sex selection is cited as a priority by the Gujarat Ministry of Health (403), suggesting that efforts are likely to promote gender equality.

3.3 Link to literature

Findings from this dissertation are consistent with previous work that zinc and ORS are likely to be cost-effective for treating acute diarrhea in children under 5 in a community setting (70). It

[59] This ranking is an improvement from 132nd in the 2010 report

emphasizes the importance of a delivery strategy that uses a variety of service providers, and in its innovative engagement of the private sector. The cost-effectiveness of DAZT was more attractive than what was found in the Haryana trial, despite a smaller incremental increase in zinc coverage, because program costs per million people were much lower ($70,542 in DAZT and $477,034 in Haryana), and cost savings per caregiver were higher ($1.45 in DAZT and $1.32 in Haryana).[60] A model by Robberstad et al (2004) did not account for transportation for caregivers or wages lost, as well as assumed fixed prescribing patterns (99). Likewise, the ORASEL trial evaluation did not account for these factors (132).

The impact of studies evaluating the cost-effectiveness analysis of zinc in the academic literature has remained limited, with around 30 citations of the most-cited study in the last ten years (99), and even fewer citations of other studies (10 citations for Patel et al (2003) (68), 16 citations for Gregorio et al (2007) (87), and 2 citations for Patel et al (2013) (85)). However, sufficient political support has been achieved to create the POUZN, SUZY, and DAZT programs, all of which have been successful in scaling up zinc. Findings confirm that increased levels of coverage are attainable when activities extend beyond one year, although did not achieve levels attained in the Haryana study (70). An intensive trial in Bangladesh attained over 80% coverage after 7 months of implementation (242), and further research is necessary to examine what levels of coverage are achievable at scale in the long term. It is estimated that universal coverage with ORS would reduce diarrhea mortality by 93% (34), and that universal coverage with zinc would lower diarrhea mortality by 23% (50).[61] It is relevant to consider economies of scale when comparing results to other community based studies, with program costs being spread across a larger set of individuals in the DAZT program leading to the lower cost per million population.

[60] An important methodological difference in the calculations for these two studies is that the Haryana trial had a control group, allowing a difference in differences calculation.
[61] LiST calculates mortality reductions sequentially, with the percent reduction on mortality from each intervention being calculated on the remaining cohort of individuals when interventions are evaluated together.

3.1 Economic evaluation in India

Economic evaluation is not adequately considered in health systems planning in India, with only around 30 studies indicated by PubMed. However, an evaluation of evidence from the Disease Control Priorities project was conducted in 2007 (147), and further research is being done by the DCP research team in the Indian context with state of the art methods (165, 167). The formation of a Health Technology Assessment body based on the model of the National Institute of Health and Care Excellence in the UK is likely to increase the importance of economic evaluation in the public sector, and the relevance of findings from this dissertation.[62]

Health Technology Assessment internationally has been advocated as a strategy for achieving universal health coverage, both directly through national HTA bodies, and through knowledge transfer from countries with more developed organizations (404). These organizations increase the relevance of cost-effectiveness evidence. As Rudolf Klein stated, ‘unless we strengthen our institutional capacity to analyze evidence, to clarify policy choices and to promote informed debate, generating more information is more likely to compound confusion than lead to better decision making’ (154). Importantly, evidence based policy making must take into account the local context. Hass argues that maximizing health may not be consistent with the objectives of Indian health systems planners whose decision making processes may be tied to eastern philosophy, where balance may take priority over maximization (180); however, people have been shown to value equity in a wide range of contexts (405), and research is needed to fully understand what factors are relevant in India.

[62] https://www.gov.uk/government/world-location-news/uk-and-india-to-work-together-on-evidence-informed-healthcare-policy-and-practice

3.2 Strengths and limitations

Overall, this dissertation has several strengths and limitations. The size of the dataset provided sufficient power to test hypotheses, although exceeded the limit required by some statistical tests such as tests for normality. In addition, risk of type 1 error exists when calculating regression coefficients in large datasets, which was particularly relevant for the net-benefit regression. The study design was valid given that it would not be ethical to conduct a controlled study on zinc given its proven effectiveness (50). In addition, introducing zinc at scale is consistent with policy in India to provide zinc to children older than 2-3 months. The broad case mix of the study and statistical methods facilitate subgroup analysis and generalizability, although from a policy perspective universal coverage of zinc has been advocated (278).

Measures of effectiveness are complicated by intrinsic limitations of the uncontrolled before and after study design (262). Secular trends such as improvements in living conditions, access to safe water, and improved sanitation may have contributed to the decline in diarrhea prevalence in the DAZT study area (406).[63] In addition, this study design is sensitive to sudden changes in the conditions of the study area (407). The Hawthorne effect is a potential confounder, which may have overstated the magnitude of the effect (262), consistent with results from a meta-analysis comparing controlled and uncontrolled studies (262, 407). Regression towards the mean may be problematic (263), which means that if a study had high diarrhea prevalence at beginning, future measurements will be likely to be less extreme. The DAZT study found a 14% prevalence of diarrhea in 2011, while levels were 13% in in 2005/6 in Gujarat (26), and were 9% nationwide (16). Regression to the mean predicts that the prevalence would be lower in future surveys as downward changes would be more frequent than upward changes.

[63] It is not possible that reductions in diarrhea were due to scaling up the rotavirus vaccine as it has only been approved in India – it has not been rolled out yet.

Data were based on self-report, which may have introduced reporting bias into our data, although recall bias was minimized by limiting the period of interest to the two weeks before the study, and the in-person questionnaire may have helped aid the memories of respondents. Only rural areas are represented in the sampling frame, although rural areas are the main settings in which the availability of zinc must be improved (38). There are no national standards for economic evaluation in India, and it is difficult to target recommendations to specific bodies, although many characteristics of international texts (102, 133, 155) and reporting standards (221, 408) are similar. In addition, the extent to which policy makers will balance these recommendations with their own value judgments and other decision making criteria must be determined. The statistical methods of this analysis may be difficult for some policy makers to understand, and care must be taken to ensure that main messages are understandable to target audiences.

3.1 Areas for further research

This dissertation has contributed to the growing body of knowledge on the economics of diarrhea interventions in India (68, 70, 85, 95, 147), and South Asia (4). However it does not fully answer several important questions. An important finding is that expenditures on medicines other than zinc and ORS were reduced, although no investigation was made about what proportion of antibiotics were prescribed for dysentery and what proportion were prescribed in excess. Further, detail was not pursued on the specific reasons for lost wages, or types of transportation that were used in seeking treatment. It can be argued that explanation of these results is less important than observing that they occurred, although further detail could be provided to promote the program in specific terms to policy makers.

Further research should be done to understand qualitative reasons for heterogeneity in prescribing practices between providers, and to what degree these practices were maintained or spread further after the end of the program. The question remains whether costs will be further reduced, and whether coverage levels will plateau in a sigmoidal curve shape (as assumed by WHO costing of child health interventions (368)), and whether the level will be substantially below 100%. Evidence to deepen understanding of the relative merits of provision through the public and private sectors and what factors influenced prescription of zinc would be informative for policy making.

The net benefit regression of this analysis required more advanced methods than the ordinary least squares approach used in the original Hoch et al (2002) article (86). Further methods have been developed that could be tested for fit and applicability. Willan et al (2004) developed a seemingly unrelated regression framework to allow for different covariates and functional forms for cost and effects regressions (285), and a similar method (conditional mixed process) could be used in our dataset given its binary effectiveness variable (409). However, these approaches assume that costs and effects are normally distributed. To relax this assumption, Nixon and Thompson (2005) (286) developed a set of Bayesian methods that allow for skewness in cost data, and consider costs and effects jointly.

For the bundled cost-effectiveness analysis, additional modeling could be undertaken to represent efficiencies gained by providing services jointly, and cost-benefit analysis could be used to consider interventions not provided by the health sector (e.g. WASH interventions). The Excel based model could be made interactive, according to precedent (236), to allow decision makers to adjust parameters according to scenarios that reflect their thinking. Alternatively, the probabilistic modeling approach could be incorporated into the LiST tool.

A systematic review of the available cost-effectiveness literature in the Indian context is necessary, as was performed in Thailand, with an emphasis on the quality of the evidence base and identification of important gaps in the literature (410). In addition, methods are necessary for guiding formal consideration of this evidence in the policy process, and creation of a national database would be useful to guide research priorities.

Modeling impact of zinc on development of drug resistance

It has been argued that overuse of antibiotics to treat diarrhea contributes to antimicrobial resistance in India and similar countries (339). However, there is a lack of studies modeling the effect of scaling up zinc on resistance to antibiotics in terms of rational use of medicines and diarrhea epidemiology. Modeling resistance is more complicated for diarrhea than for other diseases as it can be caused by a multitude of viruses, bacteria, and parasites; and since there are multiple drugs that can treat it. The most important drug to be modeled is ciprofloxacin, and the two most important pathogens are *Escherichia coli* and *Shigella*.

From the malaria literature, Coleman et al (2004) present one option for modeling the development of drug resistance (411). Initial levels of resistance can be measured from empirical studies; for example, collecting stool from a sample of children, isolating pathogenic organisms and culturing isolates on petri dishes containing antibiotics; or detecting resistant genotypes with enzyme linked assays, simple polymerase chain reactions (412), or microarrays (413). Growth trajectories for the proportion of pathogens (R) resistant to drug i at time t can be modeled using a logistic growth function using the following equation.

$$R_{it} = k\left[\frac{R_{i,0}}{R_{i,0} + (k_i - R_{i,0})\exp^{-r_i t}}\right] \tag{11}$$

$R_{i,0}$ The level of drug resistance to treatment i at the start of the N-year time period

k_i The maximum possible level of drug resistance, which cannot exceed 1 (at $k_i = 1$, the entire pathogen population would be resistant to drug i)

r_i The maximum growth rate of resistance against drug i, which occurs when $R_{i,0}$ approaches zero

Levels of resistance predicted by this equation can be used to calculate treatment failure (F)

$$F_{it} = 1 - (1 - R_{i,t})[m_i + p_i(1 - m_i)] \qquad (12)$$

m_i Probability that a patient adheres to a full regimen

p_i Probability that a patient is cured despite not fully adhering to the full course of medicine

This equation assumes that m_i and p_i remain constant over time.

The case can be made that an important difference between antibiotics to treat diarrhea and artemisinin combination therapies is that antibiotics have been used for quite some time, and historical trends for drug resistance may predict future trajectories instead of modeling according to a logistic function. However, considerable uncertainty remains about the trajectory of drug scale up for zinc, which will be a key factor in the development of drug resistance.

Alternatively, a more data intensive model could be constructed according to a Markov form including individuals in five states (Susceptible, Infected with sensitive parasites, Infected with resistant parasites, Immune, and Dead).

Rate of infection is a key parameter that would be derived from evidence on diarrhea incidence. More detailed modeling of resistance can be done based on equations representing two mechanisms - de novo development from spontaneous mutations or the spread of existing pathogens to new hosts. In addition, susceptibility can re-emerge in resistant pathogens (414). These equations would categorize fully resistant and fully susceptible populations, and model mutation and amplification rates (415). It may be considered that proliferation of resistant and susceptible populations may be different due to their levels of relative fitness (416). Level of transmission will be associated with development of host immunity to pathogens.

The fraction of the population that receives treatment would be defined by levels of intervention coverage. Successfully treated individuals return to the susceptible state, and may lose immunity. From the infected states, individuals can return to susceptible, become immune, or die. Age structure should be modeled for its influence the trajectory of resistance as fewer children are born, lowering the absolute number of episodes of child diarrhea. Which factors are most important in increasing transmission and drug resistance would be identified in sensitivity analysis. Finally, the epidemiologic model would be used to predict outcomes for a cost-effectiveness model.

3.2 Conclusion

This dissertation found that providing zinc and ORS at scale are likely to be cost saving to the health system. Expenditures by organizations to procure medicines and organize service provision are substantially offset by savings to caregivers. Econometric analysis indicates that the program is likely to be cost-effective, even when controlling for imbalances in other factors across trial phases, although limitations should be noted in the study design for detecting changes in diarrhea prevalence. The bundled analysis suggests that delivering zinc and ORS remains highly cost-effective when accompanied by other diarrhea and pneumonia interventions. Given the evidence that is available in this study, providing zinc in this rural area of India may be a good investment.

10 References

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11 Tables and figures

11.1 Introduction

Table 1. DAZT intervention components according to activity

a) Public sector

Micronutrient Initiative (MI)
Alliances: Between MI and the government. Commitment from the Department of Women and Child Development
Policy change: National Rural Health Mission (NRHM) Program Implementation Plans (PIPs) were changed to include the procurement of zinc and ORS
Training: MI trained three levels of supervisors, and supported the government in training public sector providers
Supply: Kits contained two ORS sachets and 14 taste masked zinc tablets, a measuring cup, and an informational leaflet for caregivers
Procurement: Healthy Life Pharma provided the first procurement of kits, phase 1 (2011) MI provided ORS and zinc, phase 2 (2012) MI limited to zinc only (government procured ORS), 2013 state disbursed funds to all districts to purchase zinc
Program implementation: Incentives delivered to ASHAs, Anganwadi workers (AWWs), and Auxiliary Nurse Midwives (ANMs) at monthly meetings
Distribution: ANMs informed Primary Health Center (PHC) block level supervisors about needs, supplies were redistributed from areas of surplus to areas of shortage
Monitoring and supervision: Each packet and referral was documented in a form, district coordinators routinely matched reports to data registers
Supportive supervision - Supervisors attended monthly meetings of ASHAs, AWWs, ANMs, spent at least 18 days monitoring field staff visits, provided staff with hands on training when necessary, analyzed service provider knowledge and skills, stock status, and caregiver compliance with treatment

b) Private sector

FHI-360
Alliances: Memorandums of Understanding with prominent professional medical organizations (IAP, IMA). Partnered with four NGOs, West Coast Pharmaceutical Company, and homeopathic and alternative medicine associations
Policy change: None
Training: NGO and pharma field staff were trained in diarrhea epidemiology, importance of zinc and ORS, correct dosage and regulatory guidelines, promotional strategies, role of FHI-360, and use of an SMS MIS system. Continuing medical education was provided for professional organizations. Three day residential training was provided for NGO and pharmaceutical staff
Supply: Same as public sector
Procurement: All supplies procured through the public sector
Program implementation: Push and pull strategy – push: changed prescription among key opinion leaders in the medical community, pull: NGOs created IEC materials with medical experts about diarrhea management and marketed ORS and zinc to RMPs and drug sellers
DAZT corners: staffed informational booths to create awareness and remind providers to prescribe zinc
Sehat Mitra project: In Faizabad, in-home provision by RMPs on bicycles
Monitoring and supervision: Monitor activities, validate data and reports, SMS messaging from the field
Supportive supervision: FHI staff attended monthly meetings, district coordinators spent a lot of time in the field working with new staff

IAP: Indian Academy of Pediatrics

IMA: Indian Medical Association

c) United Nations Children's Fund

UNICEF
Alliances: Sensitization workshop for field staff and NGO partners, who sensitized Rural Medical Practitioners (RMPs) and Indigenous Systems of Medical Practitioners (ISMPs) to use zinc and ORS, and established mechanisms to make supply available -Indian Academy of Pediatrics – endorsement by the state chapter published in its bulletin -Indian Medical Association - state level advocacy workshop, two district level workshops on childhood diarrhea prevention and treatment for promoting ORS and zinc. Participation of major stakeholders - state health officials, leading pediatricians, local media, and DAZT partner. Endorsement in October 2012 Bulletin of the IMA. FAQs provided by UNICEF in the IMA bulletin **Training:** Nine continuing medical education (CME) workshops with private practitioners for the use of zinc and ORS (2 with pediatricians, 7 with RMPs) **Knowledge management:** Development of a frequently asked questions booklet

Table 2. Hypothesized directions of coefficients

Variables	Odds of cost	Amount of cost	C/E	Outcome measured in literature	Source
Predisposing factors					
Demographic characteristics					
Larger household size	+	+	+	Spending	(186)
Female child	-	-	-	Care seeking from public providers Delay in care seeking Willingness to pay	(190) (191, 195) (192)
Characteristics of the social structure					
Paternal primary education	no change	-	-	Care seeking	(199, 200)
Paternal secondary education	+	-	-	Expect an education gradient	
Caregiver primary education	no change	-	-		(198)
Caregiver secondary education	+	-	-	Higher education associated with seeking care in general	(201)
Scheduled caste	-	not specified	not specified	Less likely to seek treatment	(204, 205)
Scheduled tribe	no change	not specified	not specified		
Other backwards caste	-	not specified	not specified		
Caregiver knowledge					
Knowledge about ORS	+	-	-	Care seeking	(191)
Knowledge about zinc	+	-	-		
Enabling factors					
Study phase	+	-	-	Episodes <= 4 days, DALYs averted	(99) (68, 70, 85)
Below poverty line card	-	no effect	+	Care seeking	(191)

Wealth index - 2nd quintile	+	+	not specified	Care seeking	(191, 204)
Wealth index - 3rd quintile	+	+	not specified	Cost	(95)
Wealth index - 4th quintile	+	+	not specified	Institutional delivery	(109)
Wealth index - 5th quintile	+	-	not specified		
Need factors					
Duration of diarrhea <6 days	+	+	+	Care seeking	(208)
Duration of diarrhea ≥6 days	+	+	+		
Blood in the stool	+	+	+	Care seeking	(190)
Source of care					
Public provider - facility care	+	+	+		
Public provider - community care	+	+	+		
Private provider	+	+	+		
Treatment given					
Given ORS	+	+	+		
Given zinc	+	+	+	Cost	(87)

C/E = Cost-effectiveness

Figure 1. Number of annual deaths among children under five years old due to diarrhea worldwide

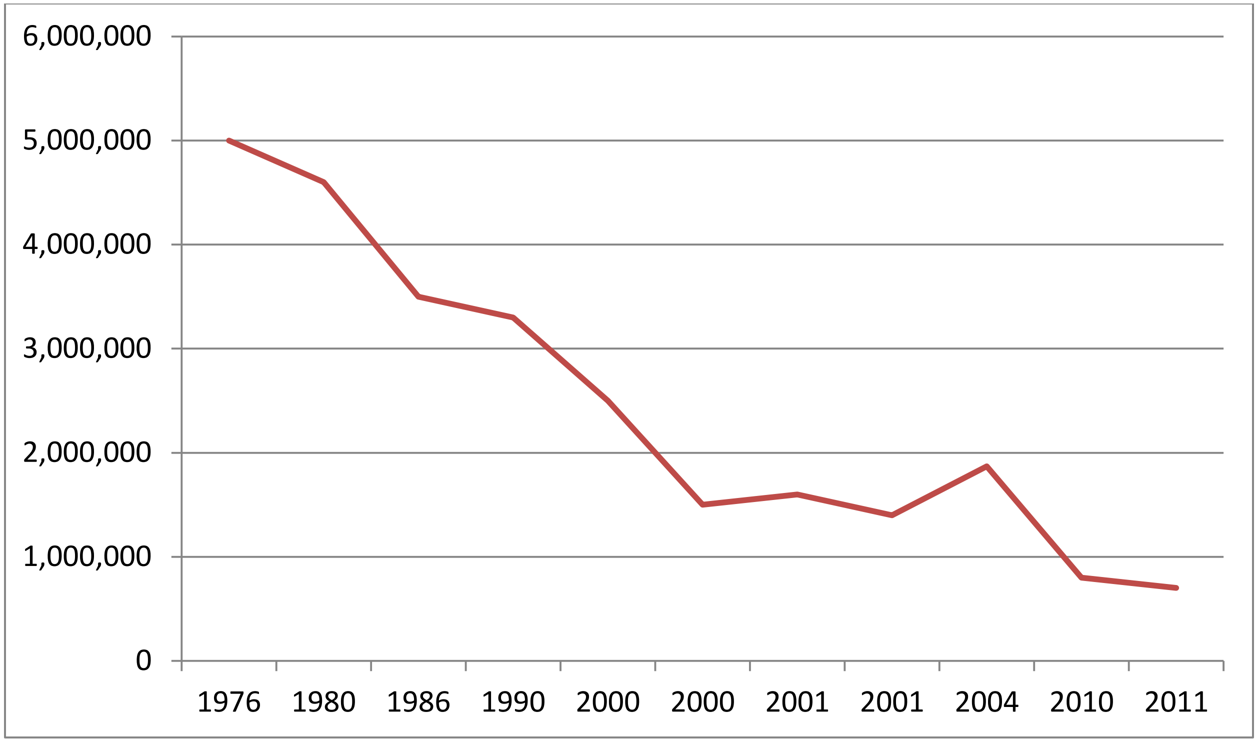


Figure 2. Progression of cost-effectiveness analysis augmented from Sculpher's framework (179)

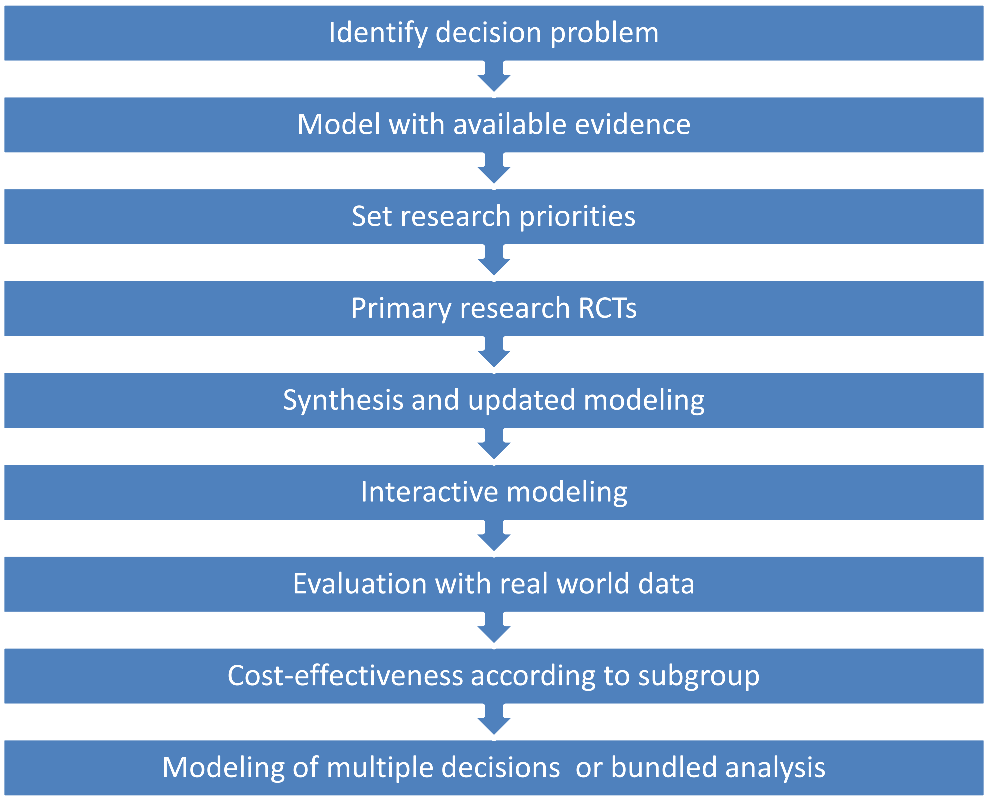
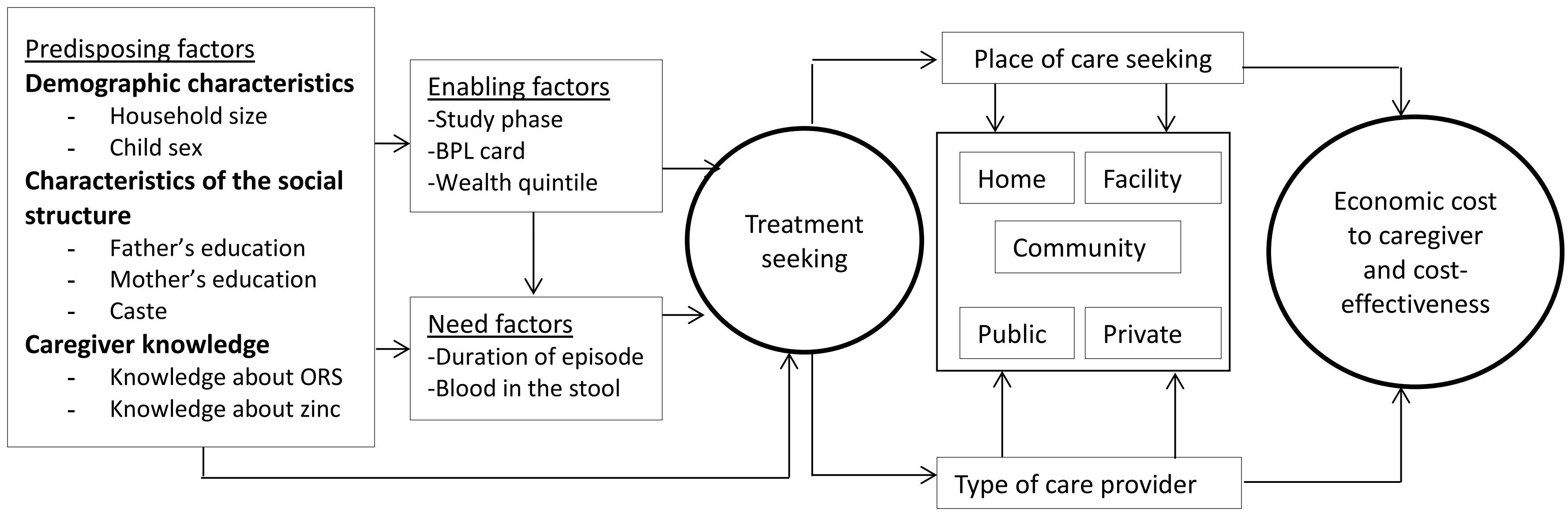


Figure 3. Conceptual framework of factors associated with costs and cost-effectiveness of diarrhea interventions in the DAZT program



11.2 Paper 1

Table 3. Population characteristics for a subsample of children under 5 with diarrhea and their caregivers interviewed in six districts of Gujarat

	Initial survey (N = 594) 22 March- 21 May 2011		Midpoint survey (N = 165) 14 Sep - 8 Oct 2012		Endpoint survey (N = 553) 29 Sep - 18 Nov 2013		F-test p-values		
Continuous variables	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Initial to midpoint**	**Initial to endpoint**	**Midpoint to endpoint**
Age of child (mo)	5.16	0.15	4.82	0.23	4.76	0.17	0.221	0.076*	0.835
Family size	6.74	0.12	6.33	0.19	6.52	0.11	0.071*	0.206	0.388
No of children in family < 5 yr	1.64	0.03	1.61	0.05	1.50	0.03	0.270	0.005**	0.095*
Age of mother	26.39	0.22	26.98	0.35	26.58	0.20	1.990	0.162	0.338
Duration of diarrhea	3.24	0.13	2.39	0.20	3.14	0.09	0.000**	0.514	0.001**
Dichotomous variables	**n**	**%**	**n**	**%**	**n**	**%**			
Child characteristics									
Age categories (mo)									
<12	594	100%	165	100%	553	100%	-	-	-
13-24	0	0%	0	0%	0	0%	-	-	-
>24	0	0%	0	0%	0	0%	-	-	-
Male gender	304	51%	95	58%	297	54%	0.155	0.377	0.417
Family characteristics									
Living mother	592	99.7%	165	100%	549	99.3%	0.456	0.364	0.279
Education of child's father									
No school	110	19%	-	-	65	12%	-	0.009**	-
Primary	484	81%	-	-	488	88%	-	0.009**	-
Secondary	243	41%	-	-	253	46%	-	0.219	-
Tertiary	39	7%	-	-	29	5%	-	0.333	-

*Marginally significant at p<0.10, **Significant at p<0.05

	Initial survey (N = 594)		Midpoint survey (N = 165)		Endpoint survey (N = 553)		F-test p-values		
Dichotomous variables (continued)	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Initial to midpoint**	**Initial to endpoint**	**Midpoint to endpoint**
Education of mother									
No school	314	53%	104	63%	325	41%	0.069*	0.003**	0.000**
Primary	280	47%	61	37%	325	59%	0.069*	0.003**	0.000**
Secondary	95	16%	16	10%	104	19%	0.089*	0.293	0.018**
Tertiary	12	2%	0	0%	11	2%	0.117	0.972	0.103
Father's occupation									
Private service	54	9%	20	12%	58	10%	0.296	0.526	0.580
Daily wage earner	264	44%	67	41%	208	38%	0.410	0.018**	0.506
Self employed	63	11%	19	12%	77	14%	0.744	0.116	0.385
Farming	202	34%	56	34%	195	35%	0.989	0.689	0.794
Does not work	1	0.17%	0	0%	1	0.18%	0.597	0.481	0.590
Mother's occupation									
Private service	2	0%	0	0%	6	1%	0.449	0.126	0.202
Daily wage earner	76	13%	28	17%	59	11%	0.221	0.294	0.049**
Self employed	2	0%	15	9%	24	4%	0.000**	0.000**	0.057*
Farming	34	6%	32	19%	77	14%	0.000**	0.000**	0.204
Does not work	476	80%	88	53%	384	69%	0.000**	0.000**	0.005**
Caste									
Scheduled caste	79	19%	31	23%	110	25%	0.370	0.105	0.370
Scheduled tribe	200	43%	10	8%	165	36%	0.001**	0.258	0.001**
Other backwards class	238	49%	100	65%	227	48%	0.034**	0.895	0.034**

*Marginally significant at $p<0.10$, **Significant at $p<0.05$

Table 4. Diarrhea prevalence, caretaker knowledge, reported symptoms, treatment received, and source of care for children under 5 in six districts of Gujarat

	Initial survey 22 Mar -21 May 2011		Midpoint 14 Sep - 8 Oct 2012		Endpoint 29 Sep - 18 Nov 2013		F-test p-values		
Variable	**n**	%	**n**	%	**n**	%	**Initial to midpoint**	**Initial to endpoint**	**Midpoint to endpoint**
Diarrhea prevalence and caregiver knowledge	N = 4202		N = 1070		N = 5080				
Diarrhea in the last two weeks	594	14.1%	165	15.4%	553	10.9%	0.476	0.000**	0.005**
Heard of ORS	2,298	54.7%	759	70.9%	3333	65.6%	0.000**	0.000**	0.041**
Heard of zinc	211	5.0%	212	19.8%	759	14.9%	0.000**	0.000**	0.019**
Breastfed in the previous 24 hours	2439	58.0%	610	57.0%	3043	59.9%	0.642	0.209	0.199
Reported symptoms associated with diarrhea in the past 14 days	N = 594		N = 165		N = 553				
Pass blood	44	7.4%	15	9.1%	34	6.1%	0.514	0.417	0.197
Fever	370	62.3%	104	63.0%	318	57.5%	0.872	0.141	0.214
Vomiting	218	36.7%	49	29.7%	199	36.0%	0.071*	0.826	0.134
Thirsty	420	70.7%	65	39.4%	167	30.2%	0.000**	0.000**	0.024**
Lethargic or irritable	382	64.3%	107	64.8%	245	44.3%	0.901	0.000**	0.000**
Sunken eyes	156	26.3%	47	28.5%	48	8.7%	0.606	0.000**	0.000**
Dehydration	268	45.1%	32	19.4%	167	30.2%	0.000**	0.000**	0.014**
Treatment received in the last two weeks	N = 594		N = 165		N = 553				
Sought external care	398	67.0%	126	76.4%	412	74.5%	0.011**	0.014**	0.626
ORS	91	15.3%	25	15.2%	219	39.6%	0.957	0.000**	0.000**
Zinc	15	2.5%	13	7.9%	124	22.4%	0.003**	0.000**	0.000**
Other medication	415	69.9%	123	74.5%	326	76.3%	0.203	0.026**	0.658
Home fluids	127	21.4%	56	33.9%	183	33.1%	0.011**	0.000**	0.883

*Marginally significant at p<0.10, **Significant at p<0.05

Variable	Initial survey		Midpoint		Endpoint		F-test p-values		
	n	%	**n**	%	**n**	%	**Initial to midpoint**	**Initial to endpoint**	**Midpoint to endpoint**
Source of care†	N = 398		N = 126		N = 412				
Any Facility (public or private)	**118**	**29.6%**	**22**	**17.5%**	**102**	**24.5%**	**0.008****	**0.194**	**0.075***
Public source - facility based	**59**	**14.8%**	**17**	**13.5%**	**78**	**18.9%**	**0.750**	**0.221**	**0.184**
PHC, gov't hospital, gov't disp.	55	13.8%	13	10.3%	72	17.5%	0.411	0.271	0.098*
ANM subcenter	4	1.0%	5	4.0%	8	1.9%	0.029**	0.283	0.224
Public source - community based	**20**	**5.0%**	**12**	**9.5%**	**83**	**20.1%**	**0.118**	**0.000****	**0.022****
Anganwadi worker/center	18	4.5%	8	6.3%	53	12.9%	0.424	0.000**	0.064*
ASHA	2	0.5%	4	3.2%	37	9.0%	0.016**	0.000**	0.031**
Private source	**319**	**80.2%**	**101**	**80.2%**	**306**	**74.3%**	**0.999**	**0.089***	**0.261**
Private doctor	227	57.0%	65	51.6%	264	64.1%	0.369	0.067*	0.023**
Nursing home/private hospital	64	16.1%	6	4.8%	27	6.6%	0.001**	0.000**	0.451
Mobile clinic	1	0.3%	0	0.0%	1	0.2%	0.575	0.981	0.582
Chemist	47	11.8%	31	24.6%	30	7.3%	0.009**	0.034**	0.000**
Traditional healer	4	1.0%	3	2.4%	5	1.2%	0.233	0.777	0.323
Charitable hospital, NGO, Trust	5	1.3%	0	0.0%	3	0.7%	0.356	0.507	0.345

†Some caregivers sought care from multiple sources, so the sum of counts for individual service providers exceed totals for their category
*Marginally significant at p<0.10
**Significant at p<0.05

Table 5. Characteristics associated with economic costs of diarrhea treatment to caregiver in six districts of Gujarat

	Initial survey 22 March - 21 May 2011					Midpoint survey 14 Sep - 8 Oct 2012					Endpoint survey 29 Sep - 18 Nov 2012				
Variable	N	Median	Mean	95% Confidence interval		N	Median	Mean	95% Confidence interval		N	Median	Mean	95% Confidence interval	
Average cost	589	$0.98	$3.71	$3.08	$4.45	165	$0.59	$4.30	$2.66	$6.99	553	$0.96	$2.26	$2.01	$2.54
Average non zero cost	353	$3.73	$5.61	$4.80	$6.53	114	$1.78	$3.44	$2.64	$4.46	327	$2.41	$3.73	$3.37	$4.09
Cost by wealth quintile															
Poorest wealth quintile	159	$0.24	$2.63	$2.03	$3.27	-	-	-	-	-	69	$0.80	$1.58	$1.06	$2.13
Very poor wealth quintile	132	$0.39	$3.02	$2.39	$3.68	-	-	-	-	-	94	$1.28	$2.17	$1.68	$2.70
Poor wealth quintile	107	$1.18	$5.17	$3.06	$8.16	-	-	-	-	-	121	$0.32	$2.24	$1.65	$2.89
Less poor wealth quintile	90	$1.40	$3.73	$2.58	$5.14	-	-	-	-	-	138	$1.24	$2.30	$1.83	$2.88
Least poor wealth quintile	96	$0.26	$4.80	$2.89	$7.07	-	-	-	-	-	130	$0.92	$2.66	$2.01	$3.34
Cost if exposed to messages	329	$1.18	$3.70	$3.00	$4.57	128	$1.14	$4.32	$2.29	$7.26	401	$0.80	$2.15	$1.84	$2.46
Cost by treatment provider															
Public facility care	59	$1.97	$3.33	$2.07	$5.29	17	$1.78	$2.28	$1.12	$3.59	78	$1.12	$2.40	$1.70	$3.30
PHC, government hospital, government dispensary	55	$2.16	$3.58	$2.23	$5.42	13	$1.96	$2.73	$1.36	$4.21	72	$1.24	$2.58	$1.80	$3.48
Auxiliary nurse midwife, subcenter	4	$0.00	$0.00	$0.00	$0.00	5	$0.00	$0.64	$0.00	$1.93	8	$0.00	$3.37	$0.00	$8.79
Public community care	20	$0.00	$2.04	$0.71	$3.66	12	$1.25	$2.62	$1.03	$4.48	83	$0.00	$1.35	$0.78	$2.06
Anganwadi worker/center	18	$0.00	$2.26	$0.79	$3.96	8	$0.42	$2.69	$0.69	$5.16	53	$0.00	$1.04	$0.55	$1.60
ASHA	2	$0.06	$0.06	$0.00	$0.12	4	$3.11	$2.48	$0.87	$4.09	37	$0.00	$2.00	$0.87	$3.70
Private source	315	$4.13	$6.47	$5.38	$7.66	101	$2.49	$6.80	$3.84	$10.59	306	$2.65	$3.87	$3.50	$4.27
Private doctor	224	$4.32	$6.33	$5.35	$7.38	65	$4.45	$7.65	$5.10	$11.03	264	$2.78	$3.81	$3.45	$4.21
Nursing home/private hospital	63	$5.70	$11.45	$7.47	$16.51	6	$6.41	$28.02	$3.44	$74.78	27	$7.74	$8.27	$6.89	$9.80
Mobile clinic	1	$5.70	$5.70	$5.70	$5.70	0	-	-	-	-	1	$1.61	$1.61	$1.61	$1.61
Chemist	47	$0.39	$2.78	$1.13	$5.37	31	$0.16	$5.58	$0.52	$15.16	30	$0.88	$2.63	$1.29	$4.27
Traditional healer	4	$0.00	$2.95	$0.00	$8.84	3	$0.07	$0.24	$0.00	$0.64	5	$0.00	$0.55	$0.00	$1.57
Charitable hospital, NGO, Trust	5	$5.80	$6.11	$1.86	$11.16	0	-	-	-	-	3	$5.62	$8.99	$1.28	$20.06

N – Number, PHC – Primary health center, ASHA – Accredited social health activist, NGO – Non-governmental organization

Table 6. Economic costs for treatment of diarrhea among children under 5 in six districts of Gujarat. Results calculated across all children with diarrhea surveyed in the study area

a) Outpatient care

Variable	Median	Mean	95% Confidence interval		Median	Mean	95% Confidence interval		Median	Mean	95% Confidence interval	
	N = 393				N = 122				N = 409			
Total cost in the last 2 weeks	$3.14	$5.11	$4.37	$6.04	$1.60	$3.21	$2.44	$4.30	$1.83	$2.98	$2.66	$3.33
Direct medical	$1.77	$2.89	$2.40	$3.56	$1.07	$1.94	$1.52	$2.48	$1.44	$2.08	$1.87	$2.33
Consultation	$0.00	$0.59	$0.46	$0.72	$0.00	$0.34	$0.19	$0.51	$0.00	$0.47	$0.38	$0.57
Dispensing	$0.00	$1.06	$0.70	$1.59	$0.00	$0.84	$0.54	$1.19	$0.00	$0.75	$0.62	$0.89
Purchase of zinc (tablets or syrup)	$0.00	$0.01	$0.00	$0.02	$0.00	$0.00	$0.00	$0.02	$0.00	$0.01	$0.01	$0.02
Purchase of ORS (packets)	$0.00	$0.02	$0.01	$0.03	$0.00	$0.00	$0.00	$0.01	$0.00	$0.02	$0.01	$0.03
Purchase of other drugs	$0.02	$1.09	$0.87	$1.32	$0.02	$0.66	$0.41	$0.98	$0.00	$0.72	$0.60	$0.86
Special food purchased	$0.00	$0.14	$0.09	$0.18	$0.00	$0.10	$0.05	$0.15	$0.00	$0.10	$0.07	$0.13
Other costs	$0.00	$0.01	$0.00	$0.02	$0.00	$0.00	$0.00	$0.00	$0.00	$0.01	$0.00	$0.01
Direct nonmedical												
Transportation (round trip)	$0.39	$0.89	$0.71	$1.09	$0.00	$0.46	$0.32	$0.62	$0.00	$0.39	$0.33	$0.46
Indirect costs*												
Wages lost	$0.00	$1.35	$1.06	$1.70	$0.00	$0.81	$0.37	$1.49	$0.00	$0.51	$0.37	$0.66

*Marginally significant at p<0.10, **Significant at p<0.05

b) Hospitalizations

Variable	Median	Mean	95% Confidence interval		Median	Mean	95% Confidence interval		Median	Mean	95% Confidence interval	
	N = 6				N = 4				N = 3			
Total cost in the last 2 weeks	$22.33	$33.09	$12.00	$56.88	$70.12	$77.16	$39.96	$118.21	$6.90	$8.32	$3.69	$14.36
Direct medical	$16.82	$19.86	$9.28	$30.42	$67.27	$64.40	$34.11	$94.70	$5.38	$5.06	$3.69	$6.10
Consultation	$1.08	$3.01	$0.43	$6.22	$0.53	$0.84	$0.00	$1.81	$0.00	$0.27	$0.00	$0.80
Dispensing	$0.00	$0.33	$0.00	$0.98	$0.00	$0.00	$0.00	$0.00	$1.61	$1.34	$0.80	$1.61
Purchase of zinc (tablets or syrup)	$0.00	$0.17	$0.00	$0.50	$0.00	$0.00	$0.00	$0.00	$0.00	$0.19	$0.00	$0.56
Purchase of ORS (packets)	$0.00	$0.07	$0.00	$0.20	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Purchase of other drugs	$3.93	$10.65	$1.64	$22.77	$22.25	$16.69	$6.02	$25.36	$1.61	$1.61	$0.00	$3.21
Special food purchased	$0.00	$0.20	$0.00	$0.52	$0.00	$0.32	$0.00	$0.96	$0.00	$0.16	$0.00	$0.48
Admission/hospitalization	$3.44	$5.11	$1.87	$9.66	$53.39	$46.55	$12.84	$80.25	$1.61	$1.50	$0.80	$2.09
Other costs	$0.00	$0.33	$0.00	$0.98	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Direct nonmedical												
Transportation (round trip)	$2.06	$3.24	$1.08	$5.96	$3.65	$8.75	$2.29	$20.66	$0.80	$0.59	$0.00	$0.96
Indirect costs												
Wages lost	$0.49	$9.99	$0.08	$22.93	$3.56	$4.01	$0.00	$8.03	$0.00	$2.68	$0.00	$8.03

*Marginally significant at p<0.10, **Significant at p<0.05

c) Home care

Variable	Median	Mean	95% Confidence interval		Median	Mean	95% Confidence interval		Median	Mean	95% Confidence interval	
	N = 195				N = 39				N = 141			
Total cost in the last 2 weeks	$0.00	$0.04	$0.00	$0.09	$0.00	$0.22	$0.00	$0.64	$0.00	$0.04	$0.00	$0.10
Direct costs only	$0.00	$0.02	$0.00	$0.05	$0.00	$0.06	$0.00	$0.15	$0.00	$0.03	$0.00	$0.08
Purchase of zinc (tablets or syrup)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Purchase of ORS (packets)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Purchase of other drugs	$0.00	$0.00	$0.00	$0.01	$0.00	$0.00	$0.00	$0.00	$0.00	$0.02	$0.00	$0.07
Special food purchased	$0.00	$0.01	$0.00	$0.02	$0.00	$0.01	$0.00	$0.02	$0.00	$0.01	$0.00	$0.02
Direct nonmedical												
Transportation (round trip)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.01	$0.00	$0.03
Indirect costs*												
Wages lost	$0.00	$0.02	$0.00	$0.06	$0.00	$0.16	$0.00	$0.49	$0.00	$0.00	$0.00	$0.00

*Marginally significant at p<0.10, **Significant at p<0.05

Table 7. Comparison of costs by source and wealth quintile to average economic costs per caregivers of children with diarrhea

	Initial survey 22 March - 21 May 2011				Midpoint survey 14 Sep - 8 Oct 2012				Endpoint survey 29 Sep - 18 Nov 2012			
	n	Cost	t test	p-value	n	Cost	t test	p-value	n	Cost	t test	p-value
Total costs#		$3.71				$4.77				$2.26		
Public source - facility care	59	$3.33	0.4353	0.3322	17	$2.52	1.5848	0.058*	78	$2.40	-0.3318	0.3704
PHC, government hospital, government dispensary	55	$3.58	0.1497	0.4407	13	$3.03	1.1622	0.1243	72	$2.58	-0.6853	0.2475
Auxiliary nurse midwife, subcenter	4	$0.00	10.7613	0.000**	5	$0.71	2.8776	0.003**	8	$3.37	-0.4185	0.344
Public source - community care	20	$2.04	1.9344	0.032**	12	$2.91	1.1798	0.1214	83	$1.35	2.4396	0.008**
Anganwadi worker/center	18	$2.26	1.5559	0.067*	8	$2.99	0.9392	0.1795	53	$1.04	3.8923	0.000**
ASHA	2	$0.06	10.4391	0.000**	4	$2.75	1.2376	0.1175	37	$2.00	0.3605	0.3602
Private source	315	$6.47	-4.0599	0.000**	101	$7.54	-1.2097	0.114	306	$3.87	-6.5375	0.000**
Private doctor	224	$6.33	-4.057	0.000**	65	$8.48	-1.7268	0.043**	264	$3.81	-6.4265	0.000**
Nursing home/private hospital	63	$11.45	-3.2186	0.001**	6	$31.07	-1.0183	0.1775	27	$8.27	-7.8231	0.000**
Mobile clinic	1	$5.70	-	-	0	-	-	-	1	$1.61	-	-
Chemist	47	$2.78	0.7494	0.2284	31	$6.19	-0.2686	0.395	30	$2.63	-0.4607	0.3241
Traditional healer	4	$2.95	0.2576	0.4065	3	$0.26	3.6422	0.000**	5	$0.55	3.264	0.013**
Charitable hospital, NGO, Trust	5	$6.11	-0.8576	0.219	0	-	-	-	3	$8.99	-1.1848	0.1788
Total cost if exposed to messages	329	$3.70	0.0296	0.4882	128	$4.79	-0.0122	0.4952	401	$2.15	0.5137	0.3038
Poorest wealth quintile	159	$2.63	2.3118	0.011**	-	-	-	-	69	$1.58	2.246	0.013**
Very poor wealth quintile	132	$3.02	1.4091	0.080*	-	-	-	-	94	$2.17	0.2943	0.3845
Poor wealth quintile	107	$5.17	-1.0627	0.145	-	-	-	-	121	$2.17	0.0456	0.4818
Less poor wealth quintile	90	$3.73	-0.0248	0.4901	-	-	-	-	138	$2.30	-0.1311	0.4479
Least poor wealth quintile	96	$4.80	-0.8984	0.1854	-	-	-	-	130	$2.66	-1.0762	0.1417
#Values against which other results from the table are compared												

*Marginally significant at p<0.10, **Significant at p<0.05

Table 8. Factors associated with the odds of economic cost of diarrhea treatment for caregivers

Conceptual framework category	Parameter	Bivariable				Multivariable (Pseudo R2 = 0.5583)			
		Odds ratio	p-value	95% conf	interval	Odds ratio	p-value	95% conf	interval
	Study phase	0.94	0.69	0.71	1.25	0.85	0.75	0.32	2.29
Demographic characteristics	Household size	1.00	0.88	0.96	1.05	0.93	0.29	0.80	1.07
	Child sex	0.89	0.34	0.71	1.13	1.39	0.46	0.58	3.35
Characteristics of the social structure	Paternal primary education	0.97	0.86	0.70	1.34	0.22	0.06*	0.05	1.05
	Paternal secondary education	1.11	0.41	0.87	1.41	0.81	0.67	0.30	2.17
	Maternal primary education	1.10	0.45	0.86	1.39	2.30	0.15	0.73	7.24
	Maternal secondary education	1.09	0.61	0.78	1.52	0.52	0.33	0.14	1.95
	Scheduled caste	0.38	0.00**	0.26	0.55	1.05	0.95	0.20	5.46
	Scheduled tribe	0.31	0.00**	0.22	0.45	0.50	0.44	0.08	2.94
	Other backwards caste	0.17	0.00**	0.11	0.26	0.25	0.11	0.05	1.39
Caregiver knowledge	Knowledge about ORS	0.99	0.92	0.78	1.25	0.57	0.23	0.23	1.41
	Knowledge about zinc	0.79	0.18	0.56	1.12	1.45	0.59	0.37	5.73
Enabling factors	Below poverty line card	1.01	0.96	0.79	1.29	0.48	0.11	0.20	1.18
	Very poor	1.11	0.44	0.85	1.47	1.21	0.82	0.24	6.11
	Poor	0.97	0.84	0.72	1.31	0.49	0.34	0.12	2.11
	Less poor	1.20	0.25	0.88	1.62	0.62	0.61	0.10	3.76
	Least poor	0.97	0.85	0.71	1.33	0.75	0.73	0.14	3.90
Need factors	Duration of diarrhea <6 days	1.40	0.10	1.23	1.60	1.76	0.00**	1.19	2.59
	Duration of diarrhea ≥6 days	0.79	0.09*	0.60	1.04	omitted			
	Blood in stool	1.57	0.10	0.92	2.66	0.63	0.59	0.12	3.41
Source of care	Public facility provider	0.26	0.00**	0.16	0.41	0.39	0.10	0.13	1.21
	Public community based provider	0.05	0.00**	0.03	0.08	0.08	0.00**	0.03	0.24
	Private provider	45.77	0.00**	25.02	83.72	37.78	0.00**	11.96	119.31
Treatment given	Given ORS	1.67	0.00**	1.20	2.33	0.87	0.79	0.31	2.43
	Given zinc	1.20	0.44	0.76	1.88	0.43	0.09*	0.16	1.15
	Constant					56.80	0.00**	6.05	533.55

*Marginally significant at p<0.10, **Significant at p<0.05

Table 9. Sensitivity analysis: Factors associated with the odds of economic cost of diarrhea treatment for caregivers

	Full education, collapsed caste				Omitted education, expanded caste				Omitted education, collapsed caste			
Parameter	Odds ratio	p-value	95% conf	interval	Odds ratio	p-value	95% conf	interval	Odds ratio	p-value	95% conf	interval
Study phase	0.95	0.91	0.37	2.42	0.62	0.32	0.25	1.57	0.72	0.49	0.29	1.81
Household size	0.92	0.22	0.80	1.05	0.91	0.17	0.79	1.04	0.90	0.14	0.79	1.03
Child sex	1.38	0.48	0.57	3.32	1.32	0.52	0.57	3.06	1.32	0.52	0.57	3.02
Paternal primary education	0.25	0.06*	0.06	1.06								
Paternal secondary education	0.83	0.70	0.32	2.15								
Mother primary education	2.20	0.15	0.76	6.37								
Mother secondary education	0.70	0.59	0.19	2.57								
Any vulnerable caste	0.41	0.27	0.09	1.98					0.49	0.34	0.11	2.14
Scheduled caste					1.14	0.86	0.26	5.05				
Scheduled tribe					0.58	0.54	0.11	3.24				
Other backwards caste					0.34	0.18	0.07	1.66				
Knowledge about ORS	0.66	0.36	0.27	1.61	0.52	0.18	0.20	1.34	0.62	0.32	0.25	1.57
Knowledge about zinc	1.37	0.64	0.37	5.06	1.37	0.61	0.41	4.62	1.39	0.57	0.44	4.41
Below poverty line card	0.50	0.12	0.21	1.21	0.56	0.19	0.24	1.34	0.57	0.19	0.25	1.31
Very poor	1.21	0.81	0.25	5.80	1.34	0.70	0.30	5.91	1.41	0.64	0.33	5.97
Poor	0.53	0.37	0.13	2.14	0.52	0.34	0.13	2.01	0.57	0.40	0.16	2.10
Less poor	0.77	0.76	0.14	4.07	0.63	0.57	0.13	3.05	0.76	0.71	0.18	3.28
Least poor	0.73	0.70	0.15	3.62	0.89	0.88	0.22	3.69	0.94	0.93	0.23	3.79
Duration of diarrhea <6 days	1.65	0.01**	1.14	2.39	1.73	0.00**	1.22	2.45	1.62	0.01**	1.15	2.28
Duration of diarrhea ≥6 days	1.00	0.00**	0.00	0.00	1.00	0.00**	0.00	0.00	1.00	0.00**	0.00	0.00
Blood in stool	0.72	0.72	0.12	4.30	0.68	0.66	0.12	3.88	0.75	0.76	0.12	4.81
Public facility provider	0.46	0.15	0.16	1.33	0.34	0.06*	0.11	1.02	0.40	0.08*	0.14	1.13
Public community based provider	0.09	0.00**	0.03	0.24	0.08	0.00**	0.03	0.24	0.08	0.00**	0.03	0.24
Private provider	37.31	0.00**	13.12	106.10	27.60	0.00**	10.07	75.63	28.29	0.00**	10.62	75.34
Given ORS	0.91	0.87	0.32	2.57	0.81	0.65	0.33	1.99	0.83	0.68	0.33	2.05
Given zinc	0.35	0.04**	0.13	0.93	0.60	0.26	0.25	1.44	0.48	0.10	0.19	1.17
Constant	34.92	0.00**	4.14	294.14	21.50	0.00**	2.94	157.08	14.75	0.01**	2.18	99.84

*Marginally significant at p<0.10, **Significant at p<0.05

Conceptual framework		Categorical maternal education, collapsed caste				Categorical paternal education, collapsed caste			
Category	Parameter	Odds ratio	p-value	95% conf	interval	Odds ratio	p-value	95% conf	interval
	Study phase	0.79	0.60	0.32	1.94	0.79	0.60	0.32	1.94
Demographic characteristics	Household size	0.91	0.18	0.80	1.04	0.91	0.18	0.80	1.04
	Child sex	1.27	0.58	0.55	2.97	1.27	0.58	0.55	2.97
Characteristics of the social structure	Maternal education categorical	0.75	0.27	0.45	1.25				
	Paternal education categorical					0.75	0.27	0.45	1.25
	Any vulnerable caste	0.42	0.28	0.09	2.03	0.42	0.28	0.09	2.03
Caregiver knowledge	Knowledge about ORS	0.65	0.35	0.26	1.60	0.65	0.35	0.26	1.60
	Knowledge about zinc	1.59	0.48	0.45	5.65	1.59	0.48	0.45	5.65
Enabling factors	Below poverty line card	0.55	0.17	0.23	1.29	0.55	0.17	0.23	1.29
	Very poor	1.50	0.59	0.35	6.40	1.50	0.59	0.35	6.40
	Poor	0.60	0.44	0.16	2.18	0.60	0.44	0.16	2.18
	Less poor	0.89	0.89	0.19	4.24	0.89	0.89	0.19	4.24
	Least poor	1.03	0.96	0.26	4.16	1.03	0.96	0.26	4.16
Need factors	Duration of diarrhea <6 days	1.62	0.01**	1.15	2.28	1.62	0.01**	1.15	2.28
	Duration of diarrhea ≥6 days	1.00	0.00**	0.00	0.00	1.00	0.00**	0.00	0.00
	Blood in stool	0.71	0.71	0.12	4.18	0.71	0.71	0.12	4.18
Source of care	Public facility provider	0.41	0.10	0.14	1.20	0.41	0.10	0.14	1.20
	Public community based provider	0.08	0.00**	0.03	0.23	0.08	0.00**	0.03	0.23
	Private provider	29.13	0.00**	10.74	79.04	29.13	0.00**	10.74	79.04
Treatment given	Given ORS	0.83	0.69	0.33	2.08	0.83	0.69	0.33	2.08
	Given zinc	0.41	0.07*	0.16	1.07	0.41	0.07*	0.16	1.07
	Constant	22.10	0.00**	2.82	173.52	22.10	0.00**	2.82	173.52

*Marginally significant at p<0.10, **Significant at p<0.05

Table 10. Sensitivity analysis according to variables tested in Rheingans et al (2012) (95)

	Logistic regression (Pseudo R2 = 0.0523)				GLM Gamma			
Parameter	Odds ratio	p-value	95% conf	interval	Coeff	p-value	95% conf	interval
Study phase	0.73	0.13	0.48	1.10	-$1.36	0.01**	-$2.32	-$0.39
Very poor	1.80	0.06*	0.97	3.36	$0.15	0.79	-$0.91	$1.20
Poor	1.31	0.36	0.73	2.37	$1.46	0.07*	-$0.13	$3.05
Less poor	0.96	0.91	0.52	1.79	$0.05	0.95	-$1.47	$1.57
Least poor	1.57	0.18	0.81	3.03	$1.06	0.08*	-$0.14	$2.25
Female child	1.00	0.99	0.69	1.44	-$0.20	0.68	-$1.15	$0.75
Paternal primary education	1.10	0.73	0.64	1.90	$0.48	0.68	-$1.84	$2.81
Paternal secondary education	1.02	0.95	0.65	1.59	$0.19	0.68	-$0.73	$1.12
Mother primary education	1.08	0.72	0.71	1.63	-$1.37	0.05*	-$2.73	$0.00
Mother secondary education	0.86	0.59	0.49	1.49	$0.58	0.24	-$0.39	$1.54
Age of child	1.08	0.01**	1.02	1.15	$0.02	0.74	-$0.11	$0.15
Blood in stool	1.94	0.12	0.84	4.50	$1.03	0.27	-$0.80	$2.86
Duration of diarrhea <6 days	1.51	0.00**	1.31	1.73	$0.56	0.02**	$0.08	$1.04
Duration of diarrhea ≥6 days	0.49	0.00**	0.33	0.71	$8.20	0.12	-$2.10	$18.49
Constant	1.35	0.37	0.71	2.57	$4.81	0.00**	$2.76	$6.86

*Marginally significant at p<0.10, **Significant at p<0.05

Table 11. Factors associated with the amount of economic cost to caregivers for diarrhea treatment

Conceptual framework category	GLM Gamma	Bivariable				Multivariable			
		Coef	p-value	95% conf	interval	Coef	p-value	95% conf	interval
	Study phase	-$1.88	0.00**	-$2.89	-$0.88	-$1.49	0.03**	-$2.80	-$0.17
Demographic characteristics	Household size	-$0.11	0.27	-$0.32	$0.09	-$0.02	0.91	-$0.43	$0.38
	Child sex	-$0.55	0.31	-$1.60	$0.50	$0.13	0.77	-$0.73	$0.99
Characteristics of the social structure	Paternal primary education	$0.47	0.46	-$0.76	$1.70	$0.17	0.76	-$0.96	$1.30
	Paternal secondary education	-$0.20	0.70	-$1.25	$0.84	$0.41	0.37	-$0.49	$1.30
	Mother primary education	-$1.15	0.04**	-$2.25	-$0.05	-$0.77	0.19	-$1.91	$0.38
	Mother secondary education	$0.03	0.96	-$1.00	$1.05	$0.89	0.18	-$0.42	$2.20
	Scheduled caste	-$0.27	0.64	-$1.39	$0.86	-$1.17	0.19	-$2.94	$0.59
	Scheduled tribe	-$0.08	0.88	-$1.09	$0.94	-$0.89	0.36	-$2.77	$1.00
	Other backwards caste	$0.04	0.94	-$1.14	$1.22	-$1.44	0.08*	-$3.05	$0.17
Caregiver knowledge	Knowledge about ORS	-$1.14	0.08*	-$2.39	$0.12	-$1.06	0.04**	-$2.06	-$0.05
	Knowledge about zinc	$0.66	0.26	-$0.47	$1.79	$1.28	0.10	-$0.25	$2.82
Enabling factors	Below poverty line card	$0.30	0.61	-$0.85	$1.44	-$0.34	0.42	-$1.18	$0.49
	Very poor	-$0.65	0.15	-$1.53	$0.23	$0.20	0.79	-$1.29	$1.70
	Poor	$1.33	0.22	-$0.81	$3.47	$0.33	0.83	-$2.64	$3.29
	Less poor	-$0.40	0.50	-$1.55	$0.75	-$0.32	0.72	-$2.06	$1.42
	Least poor	$0.39	0.51	-$0.76	$1.54	-$0.40	0.67	-$2.23	$1.44
Need factors	Duration of diarrhea <6 days	$0.75	0.00**	$0.28	$1.23	$0.54	0.00**	$0.23	$0.85
	Duration of diarrhea ≥6 days	$8.96	0.04**	$0.29	$17.63	$9.24	0.07*	-$0.77	$19.24
	Blood in stool	$0.92	0.23	-$0.56	$2.39	$0.87	0.46	-$1.43	$3.17
Source of care	Public facility provider	-$0.67	0.31	-$1.94	$0.61	$1.69	0.02**	$0.25	$3.13
	Public community based provider	-$0.81	0.28	-$2.28	$0.67	$0.13	0.90	-$1.85	$2.12
	Private provider	$2.60	0.00**	$1.36	$3.85	$3.16	0.00**	$2.13	$4.20
Treatment given	Given ORS	$0.90	0.19	-$0.44	$2.24	$0.94	0.08*	-$0.10	$1.99
	Given zinc	$0.20	0.70	-$0.79	$1.18	$0.74	0.43	-$1.09	$2.56
	Constant					$3.52	0.00**	$1.61	$5.43

*Marginally significant at p<0.10, **Significant at p<0.05

Table 12. Sensitivity analysis: Factors associated with the amount of economic cost to caregivers for diarrhea treatment

Conceptual framework		Categorical maternal education, collapsed caste				Categorical paternal education, collapsed caste			
Category	Parameter	Coef	p-value	95% conf	interval	Coef	p-value	95% conf	interval
	Study phase	-$1.60	0.00**	-$2.47	-$0.73	-$1.60	0.00**	-$2.47	-$0.73
Demographic characteristics	Household size	-$0.09	0.53	-$0.36	$0.19	-$0.09	0.53	-$0.36	$0.19
	Child sex	$0.33	0.43	-$0.48	$1.14	$0.33	0.43	-$0.48	$1.14
Characteristics of the social structure	Maternal education categorical	$0.25	0.15	-$0.09	$0.59				
	Paternal education categorical					$0.25	0.15	-$0.09	$0.59
	Any vulnerable caste	-$1.10	0.16	-$2.62	$0.42	-$1.10	0.16	-$2.62	$0.42
Caregiver knowledge	Knowledge about ORS	-$1.04	0.02**	-$1.90	-$0.17	-$1.04	0.02**	-$1.90	-$0.17
	Knowledge about zinc	$1.06	0.17	-$0.46	$2.59	$1.06	0.17	-$0.46	$2.59
Enabling factors	Below poverty line card	-$0.46	0.18	-$1.13	$0.21	-$0.46	0.18	-$1.13	$0.21
	Very poor	$0.03	0.96	-$0.99	$1.05	$0.03	0.96	-$0.99	$1.05
	Poor	$0.44	0.46	-$0.72	$1.60	$0.44	0.46	-$0.72	$1.60
	Less poor	-$0.09	0.85	-$0.97	$0.80	-$0.09	0.85	-$0.97	$0.80
	Least poor	-$0.52	0.30	-$1.51	$0.46	-$0.52	0.30	-$1.51	$0.46
Need factors	Duration of diarrhea <6 days	$0.52	0.03**	$0.04	$1.00	$0.52	0.03**	$0.04	$1.00
	Duration of diarrhea ≥6 days	$9.34	0.06*	-$0.53	$19.20	$9.34	0.06*	-$0.53	$19.20
	Blood in stool	$0.67	0.44	-$1.04	$2.39	$0.67	0.44	-$1.04	$2.39
Source of care	Public facility provider	$1.53	0.03**	$0.15	$2.91	$1.53	0.03**	$0.15	$2.91
	Public community based provider	$0.24	0.80	-$1.58	$2.06	$0.24	0.80	-$1.58	$2.06
	Private provider	$3.17	0.00**	$2.13	$4.21	$3.17	0.00**	$2.13	$4.21
Treatment given	Given ORS	$0.84	0.12	-$0.22	$1.89	$0.84	0.12	-$0.22	$1.89
	Given zinc	$0.60	0.36	-$0.67	$1.86	$0.60	0.36	-$0.67	$1.86
	Constant	$3.26	0.00**	$1.25	$5.28	$3.26	0.00**	$1.25	$5.28

*Marginally significant at p<0.10, **Significant at p<0.05

	Full education, collapsed caste				Omitted education, expanded caste				Omitted education, collapsed caste			
Parameter	Coeff	p-value	95% conf	interval	Coeff	p-value	95% conf	interval	Coeff	p-value	95% conf	interval
Study phase	-$1.25	0.01**	-$2.11	-$0.38	-$1.53	0.00**	-$2.41	-$0.65	-$1.38	0.00**	-$2.31	-$0.46
Household size	-$0.04	0.74	-$0.30	$0.21	-$0.05	0.43	-$0.18	$0.08	$0.03	0.43	-$0.05	$0.11
Female child	$0.22	0.56	-$0.50	$0.94	$0.24	0.58	-$0.61	$1.10	$0.60	0.23	-$0.38	$1.57
Paternal primary education	$0.24	0.59	-$0.64	$1.13								
Paternal secondary education	$0.43	0.22	-$0.26	$1.12								
Mother primary education	-$0.85	0.06*	-$1.72	$0.02								
Mother secondary education	$0.94	0.11	-$0.21	$2.09								
Any vulnerable caste	-$1.24	0.12	-$2.79	$0.31					-$1.34	0.11	-$2.98	$0.29
Scheduled caste					-$1.24	0.16	-$2.97	$0.49				
Scheduled tribe					-$0.88	0.32	-$2.60	$0.84				
Other backwards caste					-$1.60	0.05*	-$3.23	$0.02				
Knowledge about ORS	-$1.08	0.03**	-$2.07	-$0.09	-$0.87	0.10	-$1.92	$0.18	-$0.87	0.13	-$1.99	$0.26
Knowledge about zinc	$1.27	0.08*	-$0.17	$2.70	$1.25	0.07*	-$0.12	$2.63	$1.32	0.06*	-$0.06	$2.69
Below poverty line card	-$0.43	0.16	-$1.03	$0.17	-$0.31	0.35	-$0.97	$0.34	-$0.28	0.48	-$1.06	$0.50
Very poor	$0.41	0.48	-$0.71	$1.52	-$0.11	0.87	-$1.39	$1.17	$0.16	0.78	-$0.96	$1.28
Poor	$0.67	0.42	-$0.95	$2.29	$0.00	1.00	-$1.20	$1.20	$0.10	0.89	-$1.33	$1.53
Less poor	-$0.22	0.72	-$1.41	$0.97	-$0.22	0.73	-$1.46	$1.03	-$0.05	0.93	-$1.10	$1.01
Least poor	-$0.34	0.64	-$1.80	$1.11	-$0.56	0.49	-$2.14	$1.01	-$0.44	0.40	-$1.46	$0.58
Duration of diarrhea <6 days	$0.52	0.00**	$0.26	$0.79	$0.52	0.03**	$0.06	$0.98	$0.34	0.18	-$0.15	$0.83
Duration of diarrhea ≥6 days	$9.24	0.07*	-$0.61	$19.09	$9.57	0.07*	-$0.74	$19.89	$10.16	0.05*	$0.05	$20.27
Blood in stool	$0.77	0.47	-$1.33	$2.86	$0.69	0.47	-$1.18	$2.56	$0.48	0.59	-$1.24	$2.20
Public facility provider	$1.57	0.00**	$0.56	$2.58	$1.89	0.00**	$0.78	$3.00	$2.13	0.00**	$1.12	$3.13
Public community based provider	$0.03	0.97	-$1.55	$1.61	$0.27	0.79	-$1.66	$2.19	$0.14	0.88	-$1.57	$1.85
Private provider	$3.12	0.00**	$2.40	$3.85	$3.40	0.00**	$2.66	$4.14	$3.69	0.00**	$2.96	$4.43
Given ORS	$0.83	0.04**	$0.03	$1.63	$0.81	0.11	-$0.19	$1.81	$0.64	0.16	-$0.25	$1.54
Given zinc	$0.57	0.40	-$0.76	$1.91	$0.63	0.26	-$0.47	$1.73	$0.67	0.26	-$0.50	$1.84
Constant	$3.41	0.00**	$1.60	$5.21	$3.45	0.00**	$1.23	$5.66	$2.90	0.00**	$1.32	$4.48

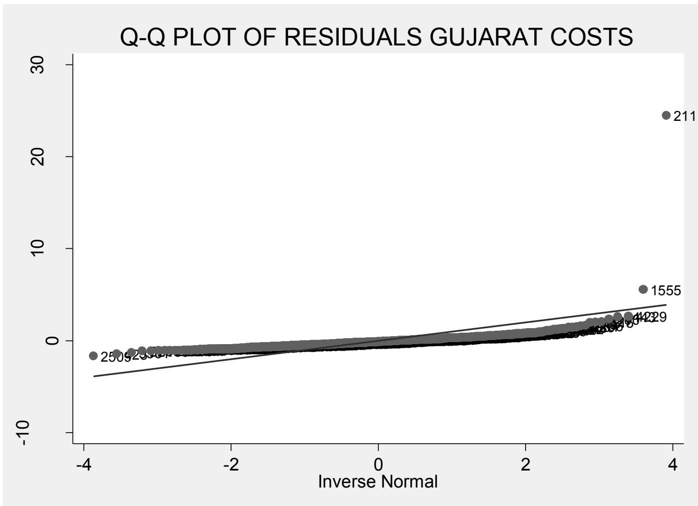
*Marginally significant at p<0.10, **Significant at p<0.05

Table 13. Economic burden of diarrhea management to caregivers per 1 million population for 1 year

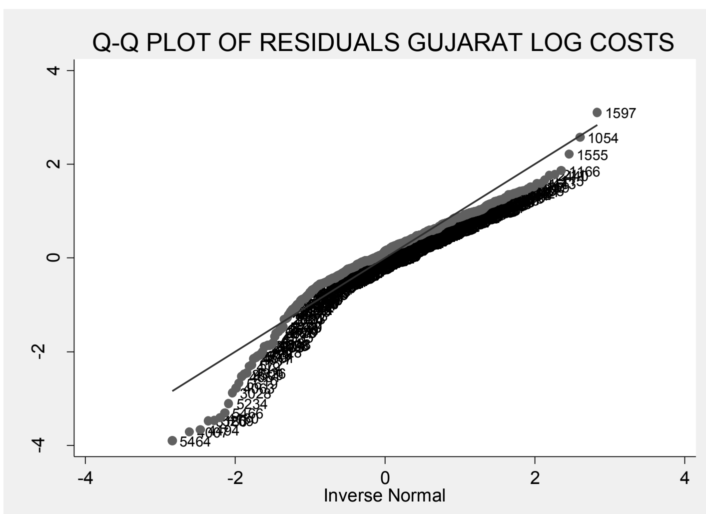
	Initial survey 22 March - 21 May 2011			Midpoint survey 14 Sep - 8 Oct 2012			Endpoint survey 29 Sep - 18 Nov 2012		
	n	**%**		**n**	**%**		**n**	**%**	
Total sample of children 2-59 months	4200			1072			5080		
Children with diarrhea in preceding 2 weeks	594	14%		165	15%		553	11%	
Cases of diarrhea in one year	15,444			4,290			14,378		
Caregivers who sought advice or treatment outside home	399	67.2%		126	76.4%		412	74.5%	
Caregivers who sought care outside the home~ Outpatient	393	66.2%		122	73.9%		409	74.0%	
Caregivers who sought care outside the home~ Hospitalizations	6	1.0%		4	2.4%		3	0.5%	
Caregivers who provided home based care	195	32.8%		39	23.6%		141	25.5%	
Out of pocket expenditures for diarrhea treatment per caregiver	**N=594**			**N=165**			**N=553**		
	n	**median**	**mean**	**n**	**median**	**mean**	**n**	**median**	**mean**
Outpatient treatment costs per patient (mean, median)	393	$3.14	$5.11	122	$1.60	$3.56	409	$1.83	$2.98
Hospitalization cost per patient (mean, median)	6	$22.33	$33.09	4	$70.12	$85.55	3	$6.90	$8.32
Home based treatment cost per patient (mean, median)	195	$0.00	$0.04	39	$0.00	$0.25	141	$0.00	$0.04
Total costs per 1 million population	**n**	**median**	**mean**	**n**	**median**	**mean**	**n**	**median**	**mean**
Total number of children < 5 per 1 million population	93,165								
Total number of cases of diarrhea per million population in one year	342,579			372,832			263,685		
Total cost		$789,987	$1,275,883		$1,075,263	$1,777,522		$366,704	$595,898
Outpatient treatment seeking	*226,656*	$712,729	$1,157,140	*275,670*	$441,525	$982,535	*195,022*	$356,832	$581,196
Hospitalizations	*3,460*	$77,258	$114,504	*9,038*	$633,738	$773,273	*1,430*	$9,872	$11,901
Home based care	*112,463*	$0	$4,239	*88,124*	$0	$21,714	*67,233*	$0	$2,801

Figure 4. Quantile-Quantile plot of studentized residuals from linear regression on costs showing non-normality in the outcome

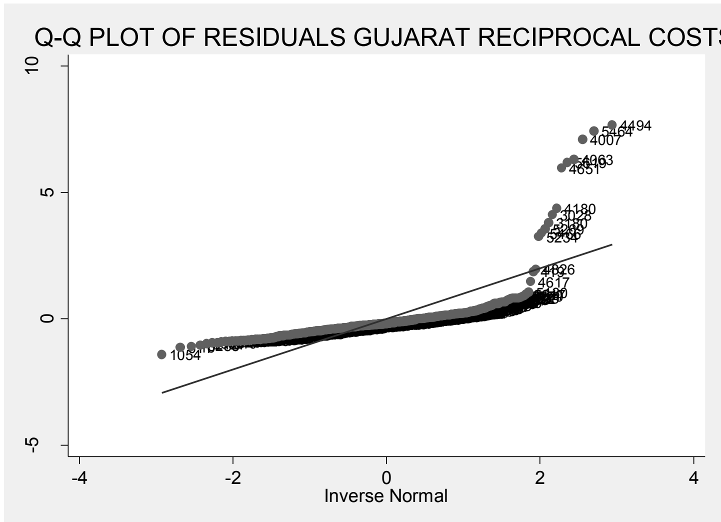
a) No transformation



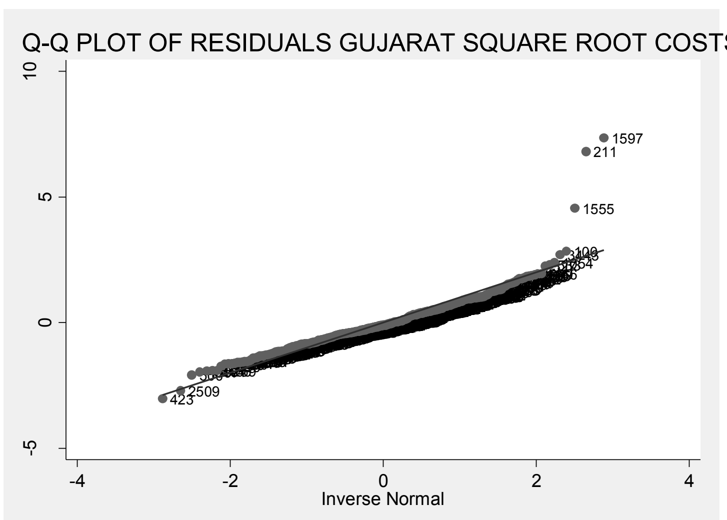
b) Log costs



c) Reciprocal cost



d) Square root cost



e) Inverse cube root cost

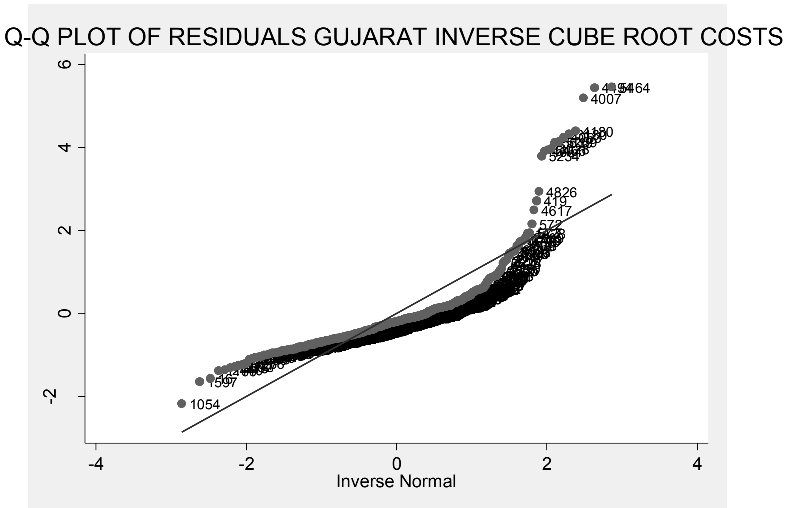


Figure 5. Residual versus fitted plot of multiple linear regression showing heteroskedasticity in the residuals

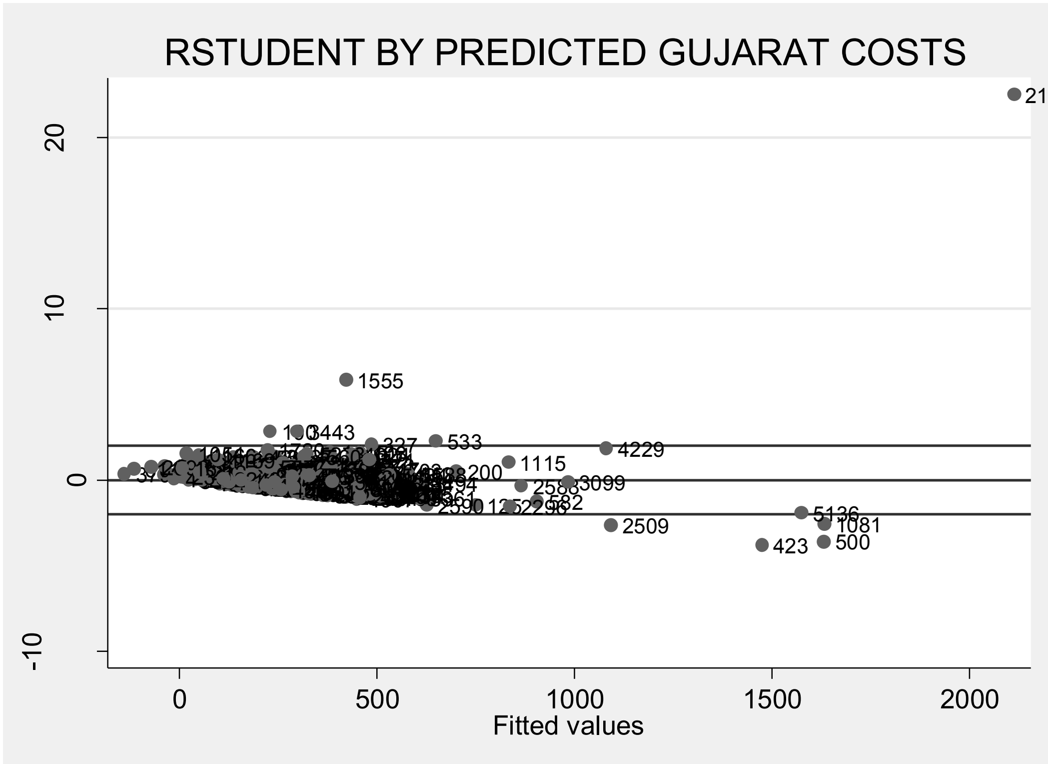
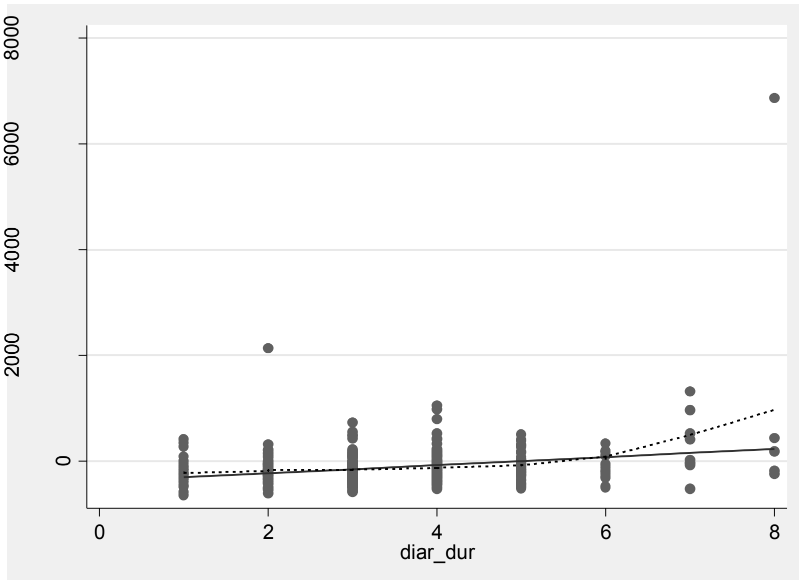


Figure 6. Locally weighted scatterplot smoothing (LOWESS) curve testing linearity of the regression line against continuous variables

1) Duration of diarrhea



2) Age of child

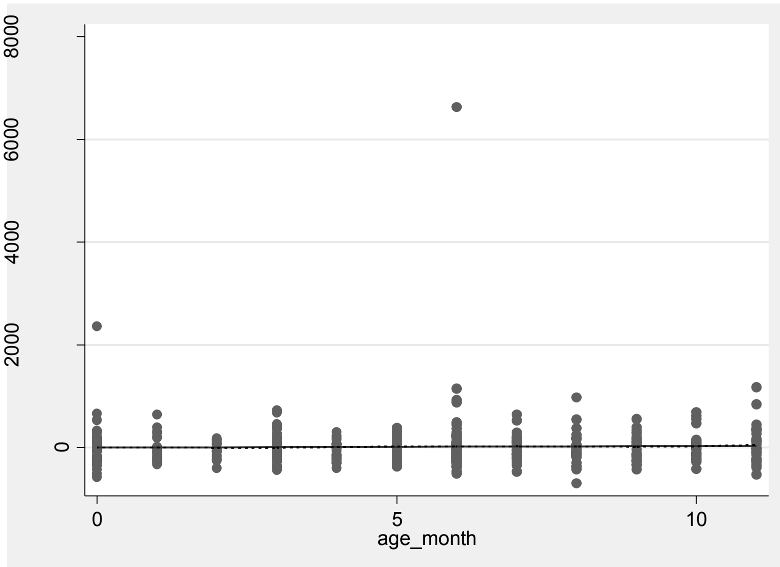


Figure 7. Histogram of factor scores from principal components analysis

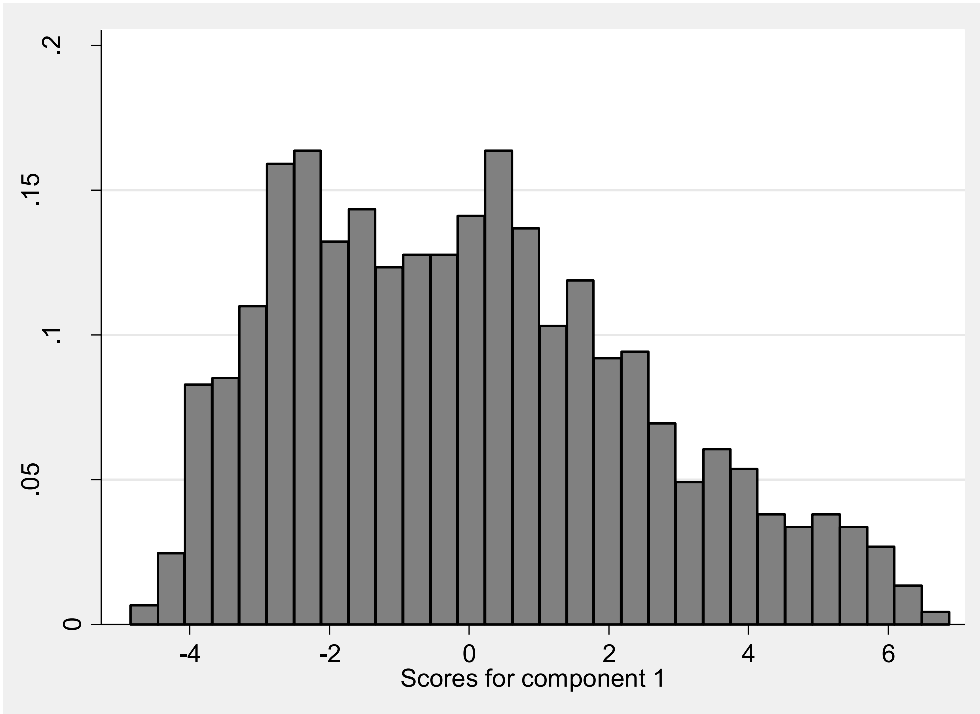


Figure 8. Component economic costs related to diarrhea treatment services to treat child diarrhea per 1 million population. The dark grey component represents direct non-medical costs, light grey component represents indirect costs, and black components represent direct medical costs. n represents the number of children that can be expected to have diarrhea among a population of 1 million for each study phase

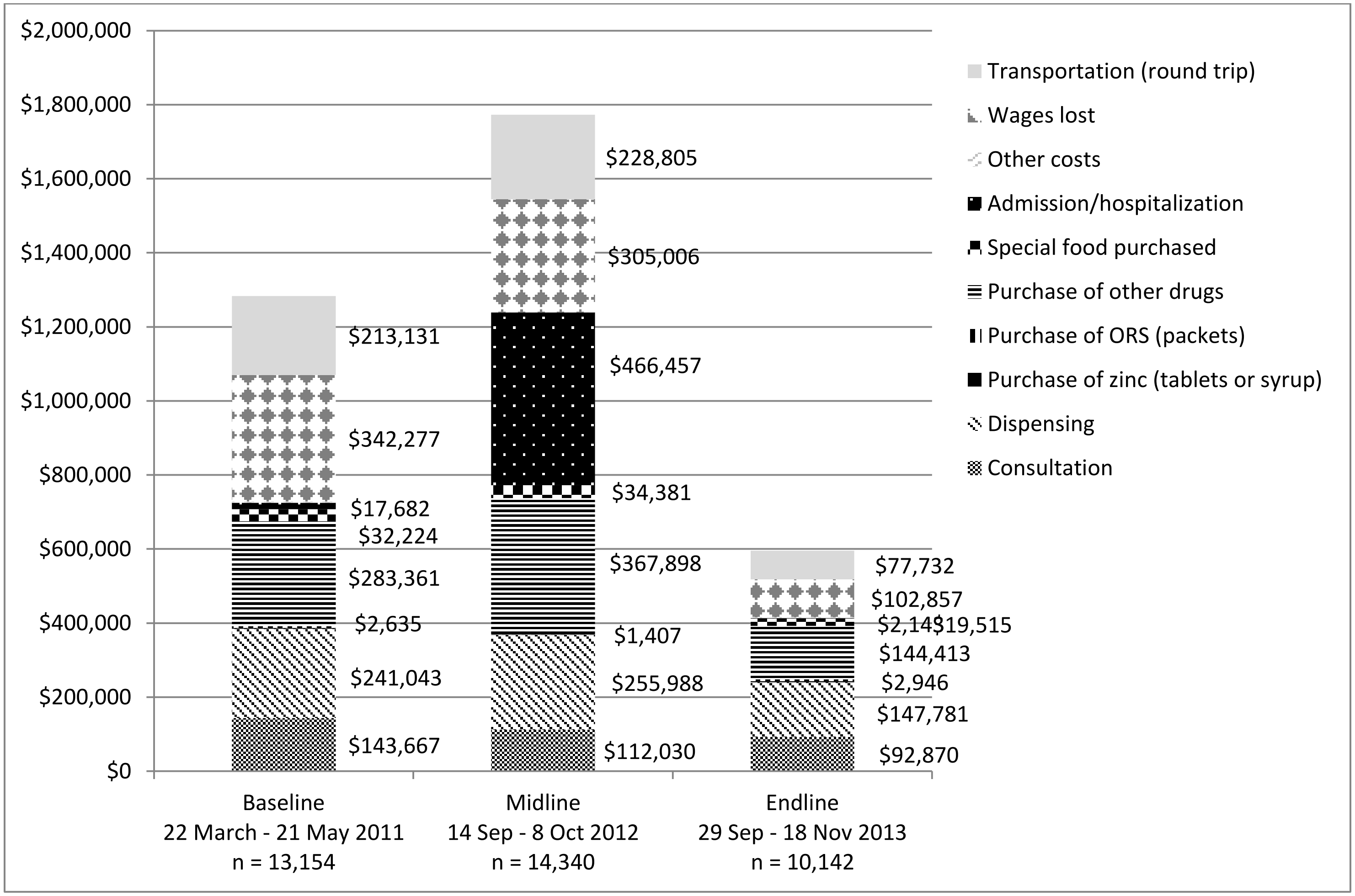


Figure 9. Box plot of economic costs on diarrhea treatment for children aged 2-59 months by provider type

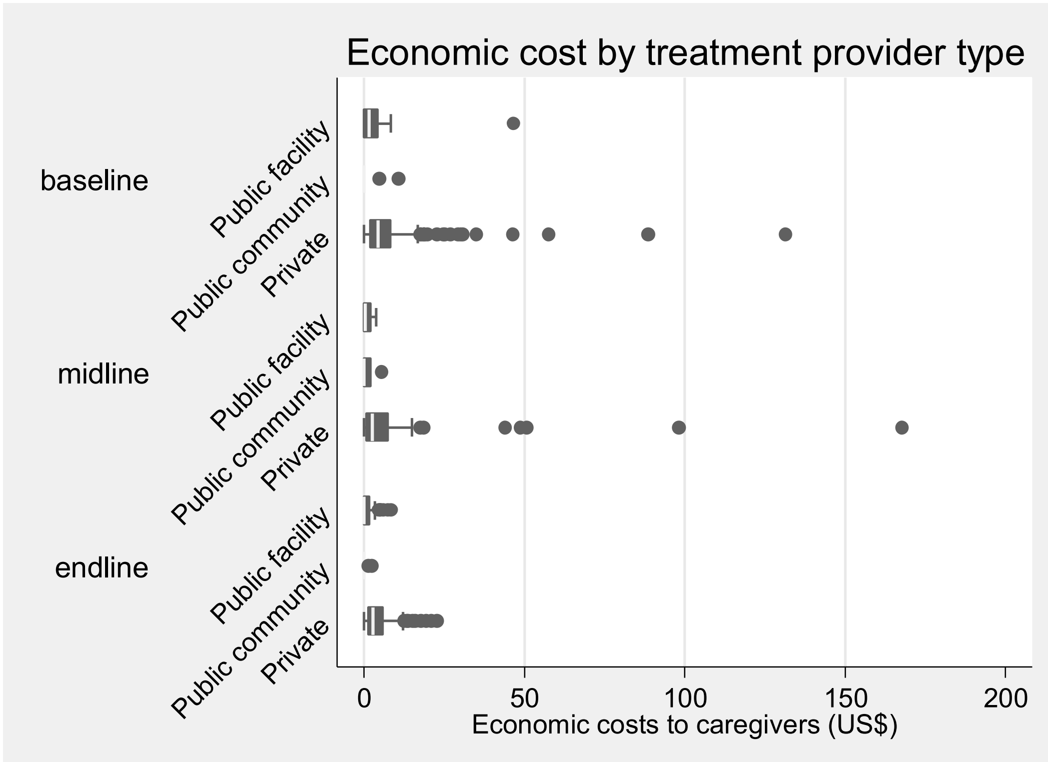
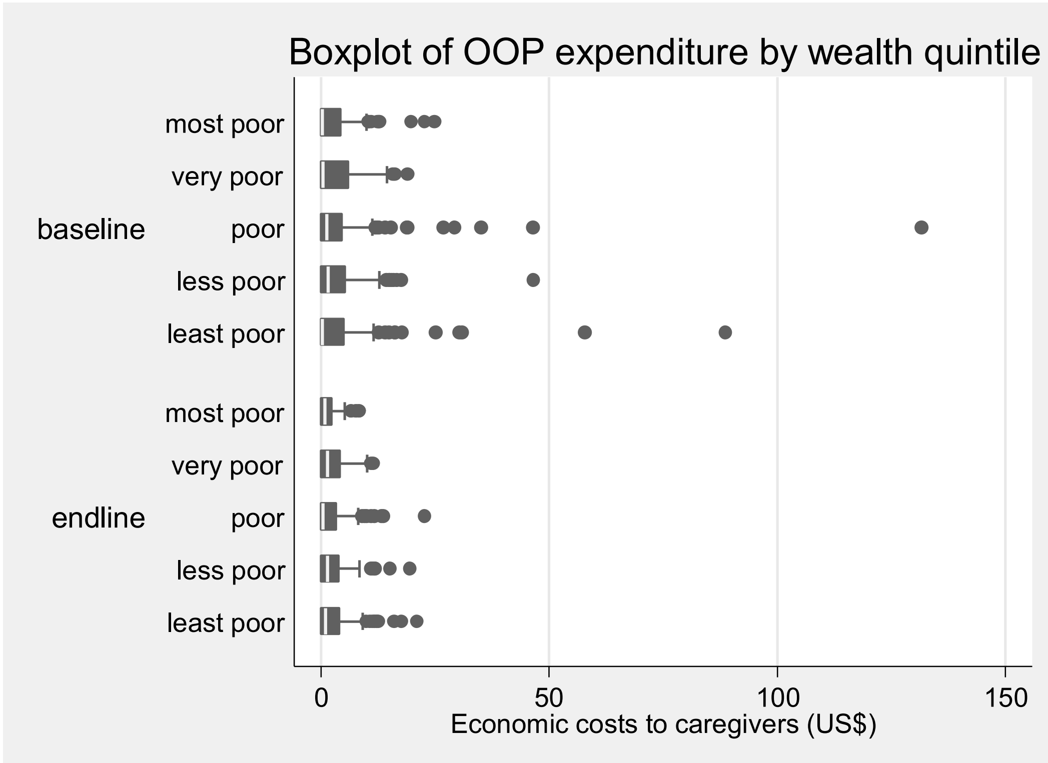


Figure 10. Box plot of economic costs on diarrhea treatment for children aged 2-59 months by wealth quintile



11.3 Paper 2

Box 1. Formula for power calculation

Formulas to calculate power with different sample sizes and different standard deviations for costs and effects in each phase (adapted from Glick et al (2011) (135) supplementary material)

Formula 1

$\Delta NMB = \Delta Q * W - \Delta C$

Formula 2

$r = n2/n1$

Formula 3

$$Z_{\beta} = \sqrt{\frac{rn_1 \Delta NMB^2}{(1+r)[(sd_{c0}{}^2 + sd_{c1}{}^2) + (W^2(sd_{q0}^2 + sd_{q1}^2)) - (2W\rho\sqrt{(sd_{c0}^2 + sd_{c1}^2)}\sqrt{sd_{q0}^2 + sd_{q1}^2}}} - Z_{\alpha/2}$$

Variables

ΔC	Expected point estimate in the difference in mean cost
ΔQ	Expected point estimate in the difference in mean effect
ρ	Correlation in the difference in cost and effect
sd c1	expected standard deviation in the cost in intervention group
sd c0	expected standard deviation in the cost in control group
sd q1	expected standard deviation for the effect in intervention group
sd q0	expected standard deviation for the effect in control group
W	maximum valuation of treatment for an episode of diarrhea
z alpha	z statistic for the type 1 error
z beta	z statistic for the type 2 error
n1	Sample size in the starting point survey
n2	Sample size in the endpoint phase

Table 14. Sample size available

Survey	Number of participants	Dates
Initial survey	4,200	Mar 22-May 21, 2011
Monsoon season		June through beginning of September*
Midpoint survey	1,072	Sep 14-Oct 8, 2012
Endpoint survey	5,080	Sep 29 -Nov 18, 2013

*Although peak diarrhea season lasts until November

Table 15. Reference case power calculation on net benefit, and sensitivity analysis on costs and effects

Parameter	Reference case	Twice effect	Half effect	No effect	Twice cost	Half cost	No cost
C	$6.03	$6.03	$6.03	$6.03	$12.06	$3.02	$0.00
Q	0.79	1.58	0.39	0	0.79	0.79	0.79
W	$14.80	$14.80	$14.80	$14.80	$14.80	$14.80	$14.80
NMB	$5.64	$17.32	-$0.19	-$6.03	-$0.39	$8.66	$11.67
ρ	0.2	0.2	0.2	0.2	0.2	0.2	0.2
sd c1	$0.85	$0.85	$0.85	$0.85	$0.85	$0.85	$0.85
sd c0	$4.17	$4.17	$4.17	$4.17	$4.17	$4.17	$4.17
sd q1	0.03	0.03	0.03	0.03	0.03	0.03	0.03
sd q0	0.04	0.04	0.04	0.04	0.04	0.04	0.04
z alpha	1.96	1.96	1.96	1.96	1.96	1.96	1.96
Starting point to endpoint (4200, 5080)							
Z_{β}	6.50	24.00	-1.67	7.08	-1.38	11.02	15.54
Power	100%	100%	95.25%	100%	91.62%	100%	100%

Table 16. Power calculation on net benefit: Sensitivity analyses on ceiling ratio, correlation coefficient, and different levels of alpha

Parameter	Different ceiling ratios					Different correlation coefficients			Different levels of alpha		
	$0.50	$3.00	$5.50	$8.00	$10.50	0.00	0.30	0.70	99%	90%	80%
C	$6.03	$6.03	$6.03	$6.03	$6.03	$6.03	$6.03	$6.03	$6.03	$6.03	$6.03
Q	0.79	0.79	0.79	0.79	0.79	0.79	0.79	0.79	0.79	0.79	0.79
W	$0.50	$3.00	$5.50	$8.00	$10.50	$14.80	$14.80	$14.80	$14.80	$14.80	$14.80
NMB	-$5.64	-$3.66	-$1.69	$0.28	$2.25	$5.64	$5.64	$5.64	$5.64	$5.64	$5.64
ρ	0.2	0.2	0.2	0.2	0.2	0.0	0.3	0.7	0.2	0.2	0.2
sd c1	0.85	0.85	0.85	0.85	0.85	$0.85	$0.85	$0.85	$0.85	$0.85	$0.85
sd c0	4.17	4.17	4.17	4.17	4.17	$4.17	$4.17	$4.17	$4.17	$4.17	$4.17
sd q1	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
sd q0	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Z_{α}	1.96	1.96	1.96	1.96	1.96	1.96	1.96	1.96	2.58	1.64	1.28
Starting point to endpoint (4200, 5080)											
Z_{β}	6.18	3.38	0.53	-1.54	1.40	5.93	6.82	8.37	5.88	6.82	7.18
Power	100%	99.96%	70.19%	6.18%	91.92%	100.00%	100%	100%	100.00%	100%	100%

Table 17. Program costs for the DAZT program according to public (MI) and private (FHI-360) sectors

	FHI-360	MI
Annualized Capital Costs		
Furniture and Equipment	$4,724	$5
Delhi	$6,976	$5
Gujarat	$1,236	$0
Trainings	$1,310	$0
Delhi	$0	$0
Gujarat	$1,310	$0
Launch Expenses	$0	$23,556
Delhi	$0	$0
Gujarat	$0	$23,556
Total Capital Costs	$6,034	$23,562
Recurrent Costs		
Personnel	$102	$282,644
Delhi	$203	$44,265
Gujarat	$0	$192,549
HO	$0	$45,830
Vehicles	$0	$19,636
Delhi	$0	$8,236
Gujarat	$0	$11,400
Buildings	$29,508	$33,021
Delhi	$42,921	$17,381
Gujarat	$8,048	$15,640
Zn and Supplies	$0	$200,393
Delhi	$0	$0
Gujarat	$0	$200,393
IEC Material	$12,295	$0
Delhi	$0	$0
Gujarat	$12,295	$0
Subcontracts	$335,101	$0
TOTAL RECURRENT COSTS	$377,005	$535,694
TOTAL ANNUALIZED PROGRAM COSTS	$383,039	$559,256
TOTAL ANNUALIZED PROGRAM COSTS PER MILLION POPULATION	$29,113	$42,507

Table 18. Descriptive statistics of the sample of children under 5 with and without diarrhea from six districts of Gujarat

a) Continuous variables

	Baseline			Endline			Statistical tests	
Variable	Mean	95% Confidence		Mean	95% Confidence		F-test	p-value
Diarrhea in the past 2 weeks	14.14%	12.82%	15.45%	10.89%	10.06%	11.71%	17.35	0.000**
Household size	6.638	6.472	6.804	6.497	6.370	6.624	2.04	0.155
Duration of diarrhea	0.22	0.19	0.25	0.20	0.18	0.23	1.04	0.310

**Significant at p<0.05, *Marginally significant at p<0.10

b) Dichotomous variables

	Baseline	Endline	Statistical tests	
Variable	Mean	Mean	F-test	p-value
Female child	45.56%	43.72%	2.719	0.101
Paternal primary education	80.27%	85.97%	13.345	0.000**
Paternal secondary education	44.43%	49.58%	4.110	0.044*
Mother primary education	51.44%	59.13%	7.518	0.007**
Mother secondary education	19.20%	22.91%	3.208	0.075*
Scheduled caste	12.22%	17.01%	4.525	0.035**
Scheduled tribe	30.67%	25.39%	1.509	0.221
Other backwards caste	41.25%	44.43%	0.701	0.404
Knowledge about ORS	54.66%	65.62%	25.260	0.000**
Knowledge about zinc	5.02%	14.94%	107.392	0.000**
Below poverty line card	40.12%	48.05%	10.637	0.001**
Blood in stool	1.04%	0.68%	3.767	0.054*
Public facility provider	1.41%	1.53%	0.1721	0.6787
Public community based provider	0.49%	1.63%	20.607	0.000**
Private provider	7.60%	6.03%	8.011	0.005**
Given ORS	2.17%	4.31%	30.485	0.000**
Given zinc	0.35%	2.45%	46.447	0.000**
Poorest wealth quintile	28.77%	12.62%	35.097	0.000**
Very poor wealth quintile	21.43%	18.69%	2.491	0.116
Poor wealth quintile	18.05%	21.48%	5.047	0.026**
Less poor wealth quintile	13.39%	25.34%	54.036	0.000**
Least poor wealth quintile	17.59%	21.83%	2.368	0.125

**Significant at p<0.05, *Marginally significant at p<0.10

Table 19. Sample statistics from deterministic economic evaluation

Group variable		Mean	SD	SE
Overall analysis				
Initial survey (N = 4200)				
Cost		$0.55	$3.55	$0.05
Effect		14.14%	34.85%	0.54%
	Correlation =	0.5477		
Endpoint survey (N = 5080)				
Cost		$0.29	$1.35	$0.02
Effect		10.89%	31.15%	0.44%
	Correlation =	0.3787		
Incremental differences between phases				
Cost difference		-$0.25		
Effect difference		-3.25%		

Table 20. Net benefit of the DAZT program relative to status quo - Simple net-benefit regression estimates

a) Generalized linear model with a gamma family and log link with Huber White robust standard errors and accounting for clustering

Variable	NB with λ = $0	NB with λ = $0.5	NB with λ = $1	NB with λ = $1.5	NB with λ = $2	NB with λ = $2.5
Constant term	0.29 [0.02] (0.00)	0.34 [0.02] (0.00)	0.40 [0.02] (0.00)	0.45 [0.02] (0.00)	0.51 [0.03] (0.00)	0.56 [0.03] (0.00)
DAZT program	1.90 [0.26] (0.00)	1.80 [0.22] (0.00)	1.73 [0.19] (0.00)	1.68 [0.17] (0.00)	1.64 [0.16] (0.00)	1.61 [0.15] (0.00)
Deviance	26598	26320	27080	27945	28788	29583
AIC	844	3625	6034	8161	10067	11793
BIC	859	3639	6049	8176	10081	11807

[se] (p-value)

b) Generalized linear model with a gamma family and an identity link with Huber White robust standard errors and accounting for clustering

Variable	NB with λ = $0	NB with λ = $0.5	NB with λ = $1	NB with λ = $1.5	NB with λ = $2	NB with λ = $2.5
Constant term	0.29 [0.02] (0.00)	0.34 [0.02] (0.00)	0.40 [0.02] (0.00)	0.45 [0.02] (0.00)	0.51 [0.03] (0.00)	0.56 [0.03] (0.00)
DAZT program	0.26 [0.07] (0.00)	0.27 [0.07] (0.00)	0.29 [0.07] (0.00)	0.31 [0.07] (0.00)	0.32 [0.07] (0.00)	0.34 [0.08] (0.00)
Deviance	26599	26321	27080	27945	28788	29583
AIC	845	3625	6034	8162	10067	11792
BIC	859	3639	6049	8176	10081	11807

[se] (p-value)

c) Generalized linear model with a gamma family and an identity link with robust standard errors

Variable	NB with λ = $0	NB with λ = $0.5	NB with λ = $1	NB with λ = $1.5	NB with λ = $2	NB with λ = $2.5
Constant term	0.29 [0.02] (0.00)	0.34 [0.02] (0.00)	0.40 [0.02] (0.00)	0.45 [0.02] (0.00)	0.51 [0.02] (0.00)	0.56 [0.03] (0.00)
DAZT program	0.26 [0.06] (0.00)	0.27 [0.06] (0.00)	0.29 [0.06] (0.00)	0.31 [0.06] (0.00)	0.32 [0.06] (0.00)	0.34 [0.07] (0.00)
Deviance	26599	26321	27080	27945	28788	29583
AIC	845	3625	6034	8162	10067	11793
BIC	859	3639	6049	8176	10081	11807

[se] (p-value)

d) Generalized linear model with a gamma family and an identity link

Variable	NB with λ = $0	NB with λ = $0.5	NB with λ = $1	NB with λ = $1.5	NB with λ = $2	NB with λ = $2.5
Constant term	0.29 [0.02] (0.00)	0.34 [0.02] (0.00)	0.40 [0.03] (0.00)	0.45 [0.03] (0.00)	0.51 [0.02] (0.00)	0.51 [0.02] (0.00)
DAZT program	0.26 [0.05] (0.00)	0.27 [0.05] (0.00)	0.29 [0.06] (0.00)	0.31 [0.06] (0.00)	0.32 [0.06] (0.00)	0.32 [0.06] (0.00)
Deviance	26599	26321	27080	27945	28788	28788
AIC	845	3625	6034	8162	10067	10067
BIC	859	3639	6049	8176	10081	10081

[se] (p-value)

e) Negative binomial model with robust standard errors and accounting for clustering

Variable	NB with λ = $0	NB with λ = $0.5	NB with λ = $1	NB with λ = $1.5	NB with λ = $2	NB with λ = $2.5
Constant term	0.22 [0.01] (0.00)	0.26 [0.01] (0.00)	0.28 [0.01] (0.00)	0.31 [0.01] (0.00)	0.34 [0.01] (0.00)	0.36 [0.01] (0.00)
DAZT program	1.58 [0.15] (0.00)	1.50 [0.12] (0.00)	1.43 [0.10] (0.00)	1.39 [0.09] (0.00)	1.35 [0.08] (0.00)	1.32 [0.07] (0.00)
Deviance	10962	11255	11949	12706	13469	14220
AIC	15397	16782	18059	19245	20353	21394
BIC	15411	16796	18073	19259	20368	21409

[se] (p-value)

f) Ordinary least squares with robust standard errors and clustering

Constant term	NB with λ = $0	NB with λ = $0.5	NB with λ = $1	NB with λ = $1.5	NB with λ = $2	NB with λ = $2.5
Constant term	0.29 [0.02] (0.00)	0.34 [0.02] (0.00)	0.40 [0.02] (0.00)	0.45 [0.02] (0.00)	0.51 [0.03] (0.00)	0.56 [0.03] (0.00)
DAZT program	0.26 [0.07] (0.00)	0.27 [0.07] (0.00)	0.29 [0.07] (0.00)	0.31 [0.07] (0.00)	0.32 [0.07] (0.00)	0.34 [0.08] (0.00)
R2	0.0025	0.0026	0.0028	0.0029	0.003	0.0031
F	14.570	15.93	17.2	18.38	19.45	20.4
Prob >F	0.000	0.0001	0.000	0.000	0.000	0.000
AIC	44012	44504	45038	45606	46200	46814
BIC	44027	44518	45052	45620	46214	46828

[se] (p-value)

g) Ordinary least squares with robust standard errors

Variable	NB with λ = \$0	NB with λ = \$0.5	NB with λ = \$1	NB with λ = \$1.5	NB with λ = \$2	NB with λ = \$2.5
Constant term	0.29 [0.02] (0.00)	0.34 [0.02] (0.00)	0.40 [0.02] (0.00)	0.45 [0.02] (0.00)	0.51 [0.02] (0.000)	0.56 [0.03] (0.000)
DAZT program	0.26 [0.06] (0.00)	0.27 [0.06] (0.00)	0.29 [0.06] (0.00)	0.31 [0.06] (0.00)	0.32 [0.06] (0.00)	0.34 [0.07] (0.00)
R2	0.0025	0.0026	0.0028	0.0029	0.003	0.0031
F	19.800	21.3	22.67	23.89	24.97	25.9
Prob >F	0.000	0.0001	0.000	0.000	0.000	0.000
AIC	44012	44504	45038	45606	46200	46813
BIC	44027	44518	45052	45620	46214	46828

[se] (p-value)

h) Net benefit of the DAZT program relative to status quo - Ordinary least squares

Variable	NB with λ = \$0	NB with λ = \$0.5	NB with λ = \$1	NB with λ = \$1.5	NB with λ = \$2	NB with λ = \$2.5
Constant term	0.29 [0.04] (0.00)	0.34 [0.04] (0.00)	0.40 [0.04] (0.00)	0.45 [0.04] (0.00)	0.51 [0.04] (0.00)	0.51 [0.04] (0.00)
DAZT program	0.26 [0.05] (0.00)	0.27 [0.06] (0.00)	0.29 [0.06] (0.00)	0.31 [0.06] (0.00)	0.32 [0.06] (0.00)	0.32 [0.06] (0.00)
R2	0.0025	0.0026	0.0028	0.0029	0.003	0.003
F	22.820	24.46	25.91	27.18	28.27	28.27
Prob >F	0.000	0.0001	0.000	0.000	0.000	0.000
AIC	44012	44504	45038	45606	46200	46200
BIC	44027	44518	45052	45620	46214	46214

[se] (p-value)

Table 21. Net benefit of the DAZT program relative to status quo - Multivariable regression GLM Gamma link log specification

Variable	NB with λ = \$0	NB with λ = \$0.5	NB with λ = \$1	NB with λ = \$1.5	NB with λ = \$2	NB with λ = \$2.5
Constant term	422.07 [405.71] (0.00)	396.98 [340.72] (0.00)	388.39 [309.13] (0.00)	388.26 [292.76] (0.00)	393.07 [284.62] (0.00)	401.01 [281.4] (0.00)
Study phase	2.44 [0.38] (0.00)	2.45 [0.34] (0.00)	2.45 [0.31] (0.00)	2.44 [0.29] (0.00)	2.43 [0.28] (0.00)	2.42 [0.27] (0.00)
Household size	1.01 [0.02] (0.53)	1.02 [0.02] (0.47)	1.02 [0.02] (0.42)	1.02 [0.02] (0.38)	1.02 [0.02] (0.35)	1.02 [0.02] (0.33)
Female child	1.01 [0.13] (0.94)	0.96 [0.11] (0.73)	0.93 [0.10] (0.52)	0.91 [0.10] (0.39)	0.90 [0.09] (0.31)	0.89 [0.09] (0.25)
Maternal education categorical	1.13 [0.08] (0.10)	1.10 [0.07] (0.16)	1.08 [0.07] (0.23)	1.06 [0.06] (0.30)	1.05 [0.06] (0.38)	1.05 [0.06] (0.45)
Scheduled caste	0.90 [0.33] (0.78)	0.88 [0.29] (0.70)	0.87 [0.26] (0.64)	0.86 [0.24] (0.58)	0.85 [0.23] (0.54)	0.84 [0.21] (0.50)
Scheduled tribe	0.86 [0.24] (0.58)	0.82 [0.21] (0.44)	0.80 [0.19] (0.36)	0.79 [0.18] (0.30)	0.78 [0.17] (0.26)	0.78 [0.16] (0.23)
Other backwards classes	1.25 [0.30] (0.36)	1.18 [0.26] (0.43)	1.15 [0.23] (0.50)	1.12 [0.22] (0.56)	1.10 [0.20] (0.61)	1.08 [0.20] (0.66)
Knowledge about ORS	1.58 [0.25] (0.00)	1.47 [0.20] (0.01)	1.40 [0.18] (0.01)	1.36 [0.16] (0.01)	1.32 [0.15] (0.02)	1.30 [0.14] (0.02)
Knowledge about zinc	1.51 [0.26] (0.02)	1.33 [0.20] (0.06)	1.23 [0.18] (0.17)	1.16 [0.17] (0.31)	1.12 [0.17] (0.47)	1.08 [0.17] (0.61)
BPL card	1.04 [0.16] (0.78)	1.05 [0.14] (0.73)	1.05 [0.13] (0.70)	1.05 [0.12] (0.68)	1.05 [0.12] (0.67)	1.05 [0.11] (0.66)
Wealth index - 2nd quintile	0.91 [0.20] (0.67)	0.93 [0.18] (0.70)	0.94 [0.17] (0.72)	0.95 [0.16] (0.75)	0.95 [0.16] (0.78)	0.96 [0.15] (0.80)

Wealth index - 3rd quintile	0.56 [0.12] (0.01)	0.58 [0.11] (0.01)	0.60 [0.11] (0.01)	0.62 [0.10] (0.00)	0.63 [0.10] (0.00)	0.64 [0.10] (0.01)
Wealth index - 4th quintile	0.68 [0.15] (0.08)	0.71 [0.14] (0.09)	0.74 [0.14] (0.11)	0.76 [0.14] (0.13)	0.78 [0.14] (0.15)	0.80 [0.14] (0.18)
Wealth index - 5th quintile	0.72 [0.23] (0.30)	0.78 [0.22] (0.37)	0.82 [0.21] (0.45)	0.86 [0.21] (0.54)	0.89 [0.21] (0.62)	0.92 [0.20] (0.71)
Duration of diarrhea	0.40 [0.02] (0.00)	0.40 [0.02] (0.00)	0.40 [0.02] (0.00)	0.40 [0.02] (0.00)	0.40 [0.02] (0.00)	0.40 [0.02] (0.00)
Blood in the stool	0.10 [0.03] (0.00)	0.11 [0.03] (0.00)	0.11 [0.03] (0.00)	0.11 [0.03] (0.00)	0.11 [0.03] (0.00)	0.12 [0.02] (0.00)
Seek treatment outside of the home	0.46 [0.12] (0.00)	0.45 [0.11] (0.00)	0.44 [0.10] (0.00)	0.44 [0.09] (0.00)	0.43 [0.09] (0.00)	0.43 [0.08] (0.00)
Given ORS	0.09 [0.01] (0.00)	0.10 [0.01] (0.00)	0.10 [0.01] (0.00)	0.11 [0.01] (0.00)	0.11 [0.01] (0.00)	0.11 [0.01] (0.00)
Given zinc	0.10 [0.03] (0.00)	0.12 [0.04] (0.00)	0.14 [0.04] (0.00)	0.15 [0.04] (0.00)	0.16 [0.05] (0.00)	0.17 [0.05] (0.00)
Deviance	15845	15995	16988	18023	18995	19892
AIC	-18951	-15240	-12198	-9610	-7353	-5349
BIC	-18808	-15097	-12056	-9467	-7210	-5206
y-hat-squared	0.000	0.000	0.005	0.071	0.382	0.989

[se] (p-value)

Table 22. Net benefit of the DAZT program relative to status quo - Multivariable regression GLM Gamma link log specification with interaction terms

Variable	NB with λ = \$0	NB with λ = \$0.5	NB with λ = \$1	NB with λ = \$1.5	NB with λ = \$2	NB with λ = \$2.5
Constant term	162.99 [170.50] (0.00)	162.35 [155.22] (0.00)	165.20 [151.43] (0.00)	169.57 [152.76] (0.00)	174.79 [156.72] (0.00)	180.54 [162.16] (0.00)
Study phase	291.45 [595.14] (0.01)	80.02 [134.64] (0.01)	50.11 [77.63] (0.01)	38.22 [56.40] (0.01)	31.90 [45.68] (0.02)	28.02 [39.33] (0.02)
Treatment-covariate interactions						
Household size	1.03 [0.07] (0.71)	1.00 [0.06] (0.97)	0.99 [0.05] (0.80)	0.98 [0.05] (0.71)	0.98 [0.05] (0.64)	0.98 [0.04] (0.60)
Female child	0.77 [0.25] (0.42)	0.79 [0.22] (0.40)	0.83 [0.21] (0.45)	0.85 [0.21] (0.51)	0.88 [0.20] (0.57)	0.89 [0.20] (0.62)
Maternal education	1.68 [0.27] (0.00)	1.48 [0.20] (0.00)	1.39 [0.17] (0.01)	1.35 [0.16] (0.01)	1.32 [0.15] (0.02)	1.30 [0.15] (0.02)
Scheduled caste	2.14 [1.28] (0.21)	1.93 [1.04] (0.22)	1.80 [0.90] (0.24)	1.71 [0.81] (0.26)	1.64 [0.75] (0.28)	1.59 [0.71] (0.30)
Scheduled tribe	2.89 [1.34] (0.02)	2.66 [1.07] (0.02)	2.45 [0.93] (0.02)	2.31 [0.84] (0.02)	2.21 [0.77] (0.02)	2.13 [0.73] (0.03)
Other backwards classes	2.22 [1.02] (0.08)	1.93 [0.77] (0.10)	1.75 [0.65] (0.13)	1.64 [0.58] (0.17)	1.55 [0.53] (0.20)	1.49 [0.50] (0.24)
Knowledge about ORS	1.75 [0.60] (0.10)	1.51 [0.42] (0.14)	1.43 [0.36] (0.16)	1.40 [0.33] (0.16)	1.38 [0.31] (0.16)	1.37 [0.30] (0.15)
Knowledge about zinc	9.51 [5.79] (0.00)	4.48 [1.95] (0.00)	3.60 [1.52] (0.00)	3.19 [1.33] (0.01)	2.95 [1.22] (0.01)	2.79 [1.14] (0.01)
BPL card	0.71 [0.20] (0.22)	0.77 [0.18] (0.27)	0.79 [0.17] (0.29)	0.80 [0.17] (0.30)	0.81 [0.17] (0.31)	0.82 [0.16] (0.33)

Wealth index - 2nd quintile	0.66 [0.33] (0.40)	0.62 [0.25] (0.24)	0.61 [0.23] (0.20)	0.61 [0.22] (0.18)	0.61 [0.22] (0.17)	0.61 [0.21] (0.16)
Wealth index - 3rd quintile	0.60 [0.25] (0.21)	0.67 [0.25] (0.28)	0.71 [0.25] (0.33)	0.74 [0.25] (0.38)	0.76 [0.25] (0.41)	0.78 [0.25] (0.43)
Wealth index - 4th quintile	0.46 [0.23] (0.12)	0.52 [0.23] (0.14)	0.56 [0.23] (0.16)	0.58 [0.23] (0.17)	0.60 [0.23] (0.19)	0.61 [0.23] (0.20)
Wealth index - 5th quintile	0.70 [0.42] (0.55)	0.79 [0.41] (0.65)	0.81 [0.39] (0.66)	0.82 [0.38] (0.67)	0.83 [0.37] (0.67)	0.83 [0.36] (0.67)
Duration of diarrhea	0.75 [0.09] (0.02)	0.89 [0.09] (0.23)	0.96 [0.08] (0.63)	1.01 [0.08] (0.95)	1.04 [0.08] (0.61)	1.07 [0.08] (0.38)
Blood in the stool	0.84 [0.58] (0.80)	0.86 [0.49] (0.79)	0.87 [0.45] (0.78)	0.87 [0.42] (0.78)	0.88 [0.40] (0.78)	0.89 [0.39] (0.79)
Seek treatment outside of the home	0.36 [0.25] (0.14)	0.52 [0.25] (0.18)	0.55 [0.24] (0.18)	0.57 [0.23] (0.17)	0.58 [0.22] (0.16)	0.58 [0.22] (0.15)
Given ORS	0.47 [0.18] (0.05)	0.61 [0.20] (0.13)	0.69 [0.20] (0.21)	0.75 [0.21] (0.30)	0.80 [0.21] (0.39)	0.83 [0.21] (0.48)
Given zinc	0.01 [0.01] (0.00)	0.04 [0.04] (0.00)	0.07 [0.05] (0.00)	0.08 [0.07] (0.00)	0.10 [0.07] (0.00)	0.11 [0.08] (0.00)
Covariates						
Household size	1.02 [0.03] (0.60)	1.02 [0.03] (0.45)	1.03 [0.03] (0.38)	1.03 [0.03] (0.33)	1.03 [0.03] (0.31)	1.03 [0.03] (0.30)
Female child	1.14 [0.14] (0.30)	1.05 [0.12] (0.67)	1.00 [0.12] (1.00)	0.97 [0.11] (0.77)	0.94 [0.11] (0.62)	0.92 [0.11] (0.52)
Maternal education	0.95 [0.07] (0.51)	0.94 [0.07] (0.42)	0.94 [0.07] (0.36)	0.93 [0.07] (0.33)	0.93 [0.07] (0.31)	0.92 [0.07] (0.29)
Scheduled caste	0.56 [0.17] (0.06)	0.59 [0.16] (0.06)	0.60 [0.16] (0.06)	0.61 [0.16] (0.06)	0.62 [0.16] (0.07)	0.63 [0.16] (0.07)

Scheduled tribe	0.49 [0.12] (0.00)	0.50 [0.11] (0.00)	0.50 [0.11] (0.00)	0.51 [0.11] (0.00)	0.52 [0.11] (0.00)	0.52 [0.12] (0.00)
Other backwards classes	0.81 [0.14] (0.24)	0.82 [0.14] (0.24)	0.83 [0.14] (0.26)	0.83 [0.14] (0.30)	0.84 [0.15] (0.33)	0.84 [0.15] (0.35)
Knowledge about ORS	1.33 [0.21] (0.07)	1.24 [0.18] (0.15)	1.18 [0.17] (0.26)	1.14 [0.17] (0.37)	1.11 [0.16] (0.48)	1.09 [0.16] (0.58)
Knowledge about zinc	1.17 [0.16] (0.25)	1.07 [0.14] (0.60)	1.01 [0.14] (0.92)	0.98 [0.14] (0.87)	0.95 [0.15] (0.73)	0.93 [0.15] (0.64)
BPL card	1.19 [0.18] (0.26)	1.17 [0.16] (0.25)	1.17 [0.16] (0.26)	1.16 [0.15] (0.27)	1.15 [0.15] (0.28)	1.15 [0.15] (0.29)
Wealth index - 2nd quintile	1.21 [0.28] (0.41)	1.23 [0.27] (0.34)	1.25 [0.28] (0.31)	1.27 [0.29] (0.29)	1.29 [0.30] (0.28)	1.30 [0.31] (0.27)
Wealth index - 3rd quintile	0.69 [0.17] (0.14)	0.70 [0.16] (0.12)	0.71 [0.16] (0.13)	0.72 [0.16] (0.15)	0.73 [0.17] (0.16)	0.74 [0.17] (0.18)
Wealth index - 4th quintile	0.97 [0.27] (0.92)	0.99 [0.26] (0.98)	1.01 [0.26] (0.96)	1.03 [0.27] (0.90)	1.05 [0.27] (0.85)	1.07 [0.28] (0.80)
Wealth index - 5th quintile	0.91 [0.25] (0.73)	0.96 [0.24] (0.86)	1.00 [0.24] (0.99)	1.03 [0.25] (0.90)	1.06 [0.26] (0.81)	1.09 [0.27] (0.73)
Duration of diarrhea	0.41 [0.02] (0.00)	0.40 [0.02] (0.00)	0.39 [0.02] (0.00)	0.39 [0.02] (0.00)	0.38 [0.02] (0.00)	0.38 [0.02] (0.00)
Blood in the stool	0.11 [0.05] (0.00)	0.12 [0.05] (0.00)	0.12 [0.05] (0.00)	0.12 [0.05] (0.00)	0.13 [0.04] (0.00)	0.13 [0.04] (0.00)
Seek treatment outside of the home	0.60 [0.23] (0.19)	0.58 [0.21] (0.13)	0.57 [0.19] (0.10)	0.56 [0.18] (0.08)	0.56 [0.18] (0.07)	0.55 [0.17] (0.05)
Given ORS	0.10 [0.02] (0.00)	0.10 [0.02] (0.00)	0.11 [0.02] (0.00)	0.11 [0.02] (0.00)	0.11 [0.02] (0.00)	0.11 [0.02] (0.00)
Given zinc	0.17 [0.06] (0.00)	0.20 [0.07] (0.00)	0.21 [0.07] (0.00)	0.23 [0.07] (0.00)	0.24 [0.07] (0.00)	0.25 [0.08] (0.00)
Deviance	15922	15984	16919	17917	18861	19735

AIC	-20245	-16066	-12850	-10169	-7856	-5815
BIC	-19973	-15795	-12579	-9898	-7584	-5544
Y hat squared	0.000	0.000	0.000	0.000	0.001	0.016

[se] (p-value)

Table 23. Net benefit of the DAZT program relative to status quo according to covariates used in Rheingans et al (2012) (95) - Multivariable regression GLM Gamma link log specification with interaction terms

Variable	NB with λ = \$0	NB with λ = \$0.5	NB with λ = \$1	NB with λ = \$1.5	NB with λ = \$2	NB with λ = \$2.5
Constant term	1.38 [1.08] (0.68)	1.38 [1.01] (0.66)	1.41 [1.00] (0.63)	1.47 [1.03] (0.59)	1.53 [1.08] (0.54)	1.60 [1.13] (0.50)
Treatment-covariate interactions						
Study phase	14.81 [18.10] (0.03)	12.84 [14.20] (0.02)	11.50 [11.94] (0.02)	10.54 [10.49] (0.02)	9.83 [9.49] (0.02)	9.27 [8.77] (0.02)
Wealth index - 2nd quintile	0.59 [0.26] (0.23)	0.58 [0.23] (0.17)	0.58 [0.21] (0.13)	0.58 [0.20] (0.11)	0.58 [0.19] (0.10)	0.57 [0.19] (0.09)
Wealth index - 3rd quintile	0.76 [0.28] (0.45)	0.76 [0.25] (0.41)	0.77 [0.23] (0.39)	0.77 [0.23] (0.38)	0.78 [0.22] (0.37)	0.78 [0.22] (0.37)
Wealth index - 4th quintile	0.55 [0.24] (0.16)	0.55 [0.21] (0.13)	0.56 [0.20] (0.11)	0.56 [0.20] (0.10)	0.57 [0.19] (0.09)	0.57 [0.19] (0.09)
Wealth index - 5th quintile	0.72 [0.37] (0.53)	0.73 [0.35] (0.52)	0.75 [0.33] (0.52)	0.76 [0.33] (0.53)	0.78 [0.32] (0.54)	0.79 [0.32] (0.56)
Female child	0.64 [0.19] (0.14)	0.70 [0.19] (0.19)	0.74 [0.18] (0.23)	0.78 [0.18] (0.28)	0.80 [0.18] (0.32)	0.82 [0.18] (0.35)
Maternal education	1.24 [0.19] (0.15)	1.23 [0.17] (0.12)	1.23 [0.16] (0.10)	1.23 [0.15] (0.09)	1.23 [0.14] (0.08)	1.22 [0.14] (0.07)
Child age	0.96 [0.04] (0.23)	0.96 [0.03] (0.23)	0.96 [0.03] (0.24)	0.97 [0.03] (0.25)	0.97 [0.03] (0.26)	0.97 [0.03] (0.28)
Blood in the stool	1.39 [0.82] (0.57)	1.37 [0.71] (0.55)	1.35 [0.64] (0.53)	1.33 [0.59] (0.52)	1.32 [0.55] (0.50)	1.31 [0.52] (0.49)
Duration of diarrhea	1.09 [0.10] (0.37)	1.11 [0.10] (0.22)	1.13 [0.09] (0.12)	1.15 [0.09] (0.07)	1.16 [0.08] (0.04)	1.17 [0.08] (0.03)

Covariates						
Wealth index - 2nd quintile	1.35 [0.34] (0.22)	1.40 [0.33] (0.15)	1.44 [0.33] (0.12)	1.46 [0.34] (0.10)	1.48 [0.34] (0.09)	1.49 [0.35] (0.09)
Wealth index - 3rd quintile	0.74 [0.18] (0.22)	0.78 [0.17] (0.26)	0.80 [0.17] (0.31)	0.82 [0.18] (0.36)	0.84 [0.18] (0.41)	0.85 [0.18] (0.45)
Wealth index - 4th quintile	0.82 [0.21] (0.42)	0.90 [0.21] (0.65)	0.96 [0.22] (0.85)	1.00 [0.23] (0.99)	1.04 [0.24] (0.87)	1.06 [0.24] (0.78)
Wealth index - 5th quintile	0.93 [0.27] (0.80)	1.01 [0.26] (0.98)	1.06 [0.27] (0.80)	1.11 [0.27] (0.68)	1.14 [0.27] (0.59)	1.16 [0.28] (0.53)
Female child	1.26 [0.21] (0.16)	1.17 [0.17] (0.30)	1.10 [0.15] (0.47)	1.06 [0.14] (0.64)	1.03 [0.13] (0.80)	1.01 [0.12] (0.94)
Maternal education	0.92 [0.10] (0.46)	0.91 [0.09] (0.36)	0.91 [0.08] (0.28)	0.90 [0.08] (0.23)	0.89 [0.08] (0.19)	0.89 [0.08] (0.16)
Child age	1.02 [0.02] (0.35)	1.02 [0.02] (0.42)	1.01 [0.02] (0.49)	1.01 [0.02] (0.54)	1.01 [0.02] (0.59)	1.01 [0.02] (0.62)
Blood in the stool	0.08 [0.03] (0.00)	0.09 [0.03] (0.00)	0.09 [0.03] (0.00)	0.09 [0.03] (0.00)	0.09 [0.03] (0.00)	0.10 [0.03] (0.00)
Duration of diarrhea	0.37 [0.02] (0.00)	0.37 [0.02] (0.00)	0.37 [0.02] (0.00)	0.37 [0.02] (0.00)	0.36 [0.02] (0.00)	0.36 [0.02] (0.00)
Deviance	19,614	19,758	20,713	21,716	22,663	23,538
AIC	-12,349	-8,984	-6,170	-3,745	-1,611	296
BIC	-12,207	-8,841	-6,027	-3,602	-1,468	439
y-hat-squared	0.000	0.000	0.000	0.000	0.001	0.015

[se] (p-value)

Table 24. GLM Gamma link log specification comparing full dataset to a specification omitting the top ten most influential observations. Note that models contained all independent covariates, but only the treatment variable is presented in this table for brevity.

	All observations			Omitting ten influential observations		
Variable	NB with λ = \$0	NB with λ = \$1	NB with λ = \$2	NB with λ = \$0	NB with λ = \$1	NB with λ = \$2
Constant term	162.99 [170.50] (0.00)	165.20 [151.43] (0.00)	174.79 [156.72] (0.00)	162.49 [170.09] (0.00)	164.53 [150.93] (0.00)	174.01 [156.13] (0.00)
Study phase	291.45 [595.14] (0.01)	50.11 [77.63] (0.01)	31.90 [45.68] (0.02)	287.59 [586.43] (0.01)	49.80 [77.09] (0.01)	31.75 [45.43] (0.02)
Deviance	15922	16919	18861	15918	16915	18856
AIC	-20245	-12850	-7856	-20228	-12838	-7846
BIC	-19973	-12579	-7584	-19957	-12567	-7575
Y hat squared	0.000	0.000	0.001	0.000	0.000	0.001

[se] (p-value)

Figure 11. Z score and power for type 2 error for the starting point to endpoint comparison according to different values for willingness to pay for one unit of health outcome. This pattern reflects pattern C depicted in Figure 1 of Glick et al (2011) part 2 (417).

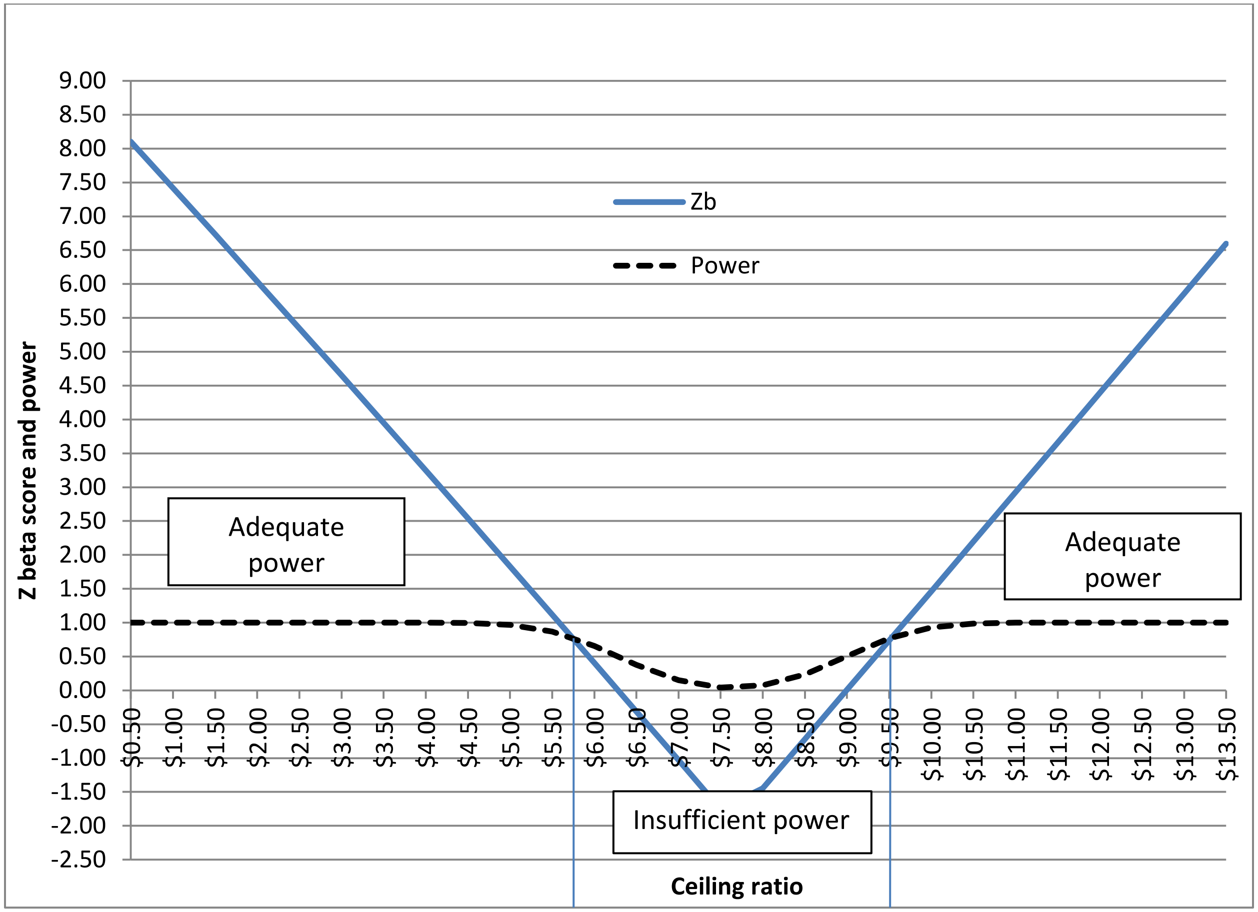


Figure 12. Cost effectiveness plane showing regions of adequate power according to incremental costs and effects (illustration from another model since stochastic results do not exist yet for the current model). Blue dots represent cost-effectiveness outputs, and black lines represent levels of willingness to pay for one unit of health outcome (λ). This figure is based on a similar figure by Briggs and Gray (1998) (134).

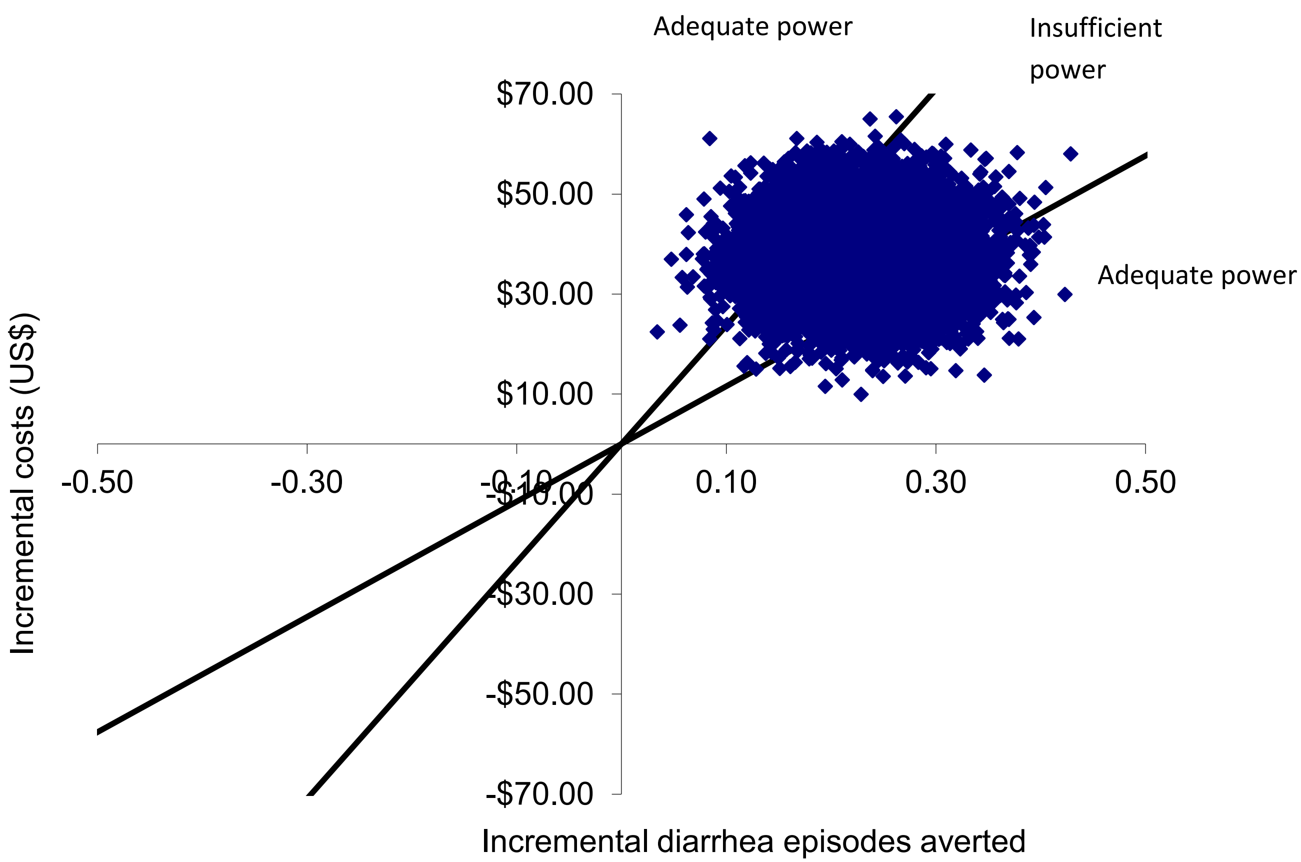


Figure 13. Cost-effectiveness acceptability curve showing the same concept as the cost-effectiveness plane in Figure 11, but emphasizing the probability that the intervention is cost-effective on the y-axis. Levels of λ that correspond with power thresholds in figures 10 & 11 are indicated with black lines on the x-axis.

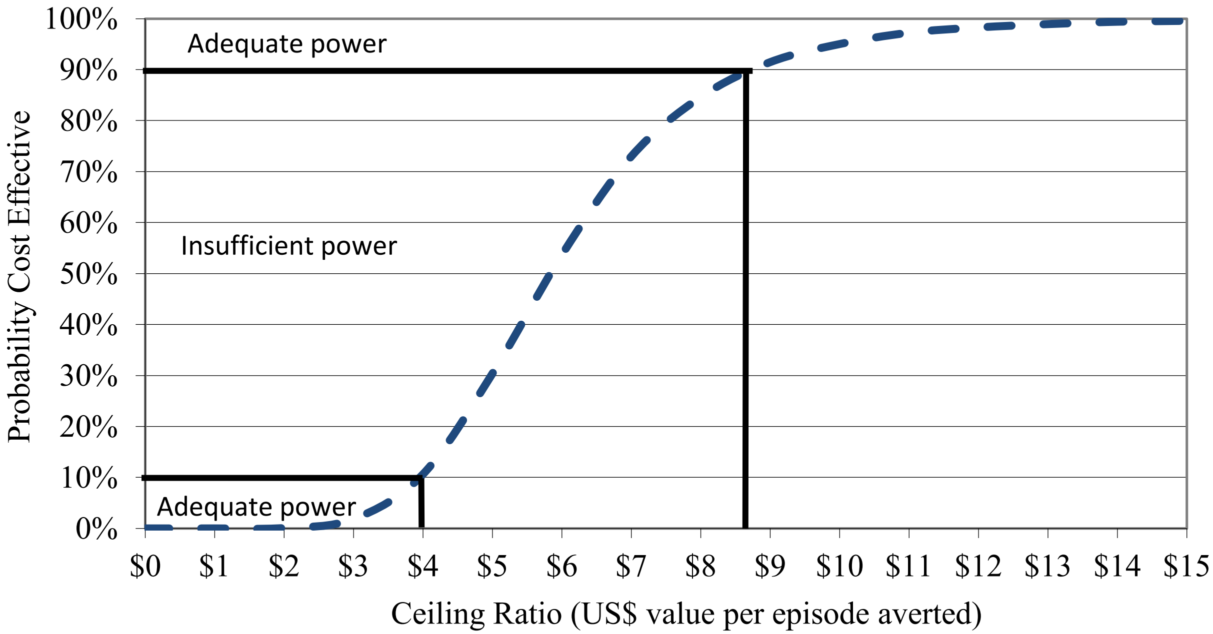


Figure 14. Quantile-Quantile plot of studentized residuals from linear regression on net benefit showing non-normality in the outcome

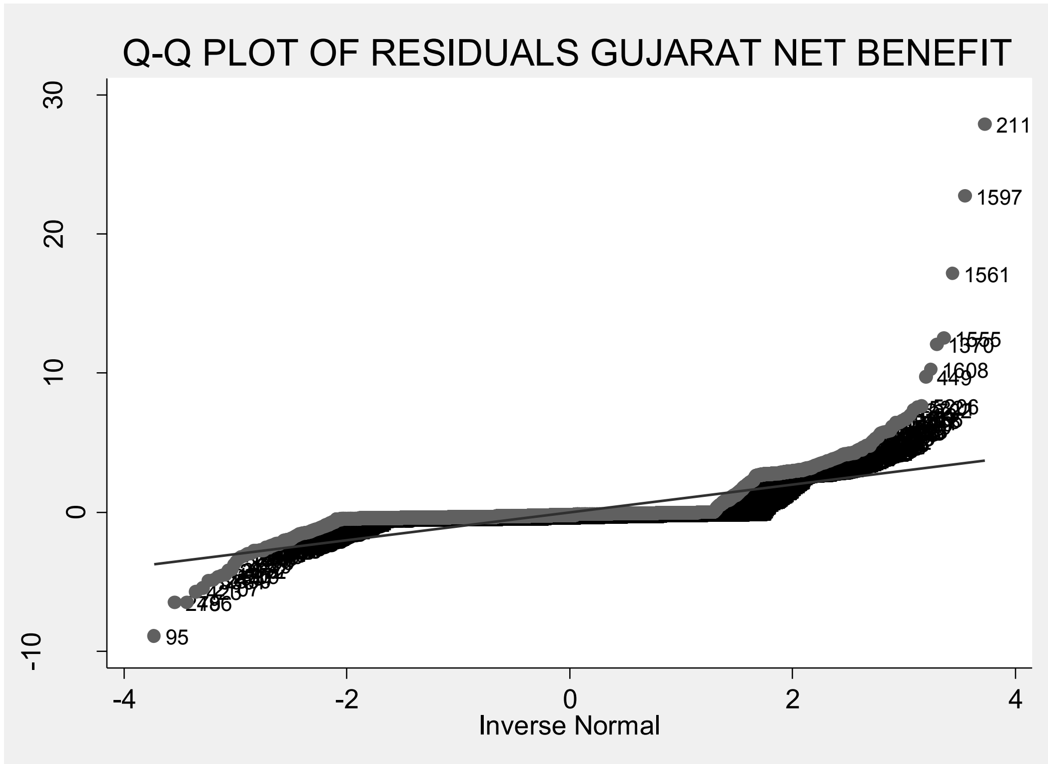
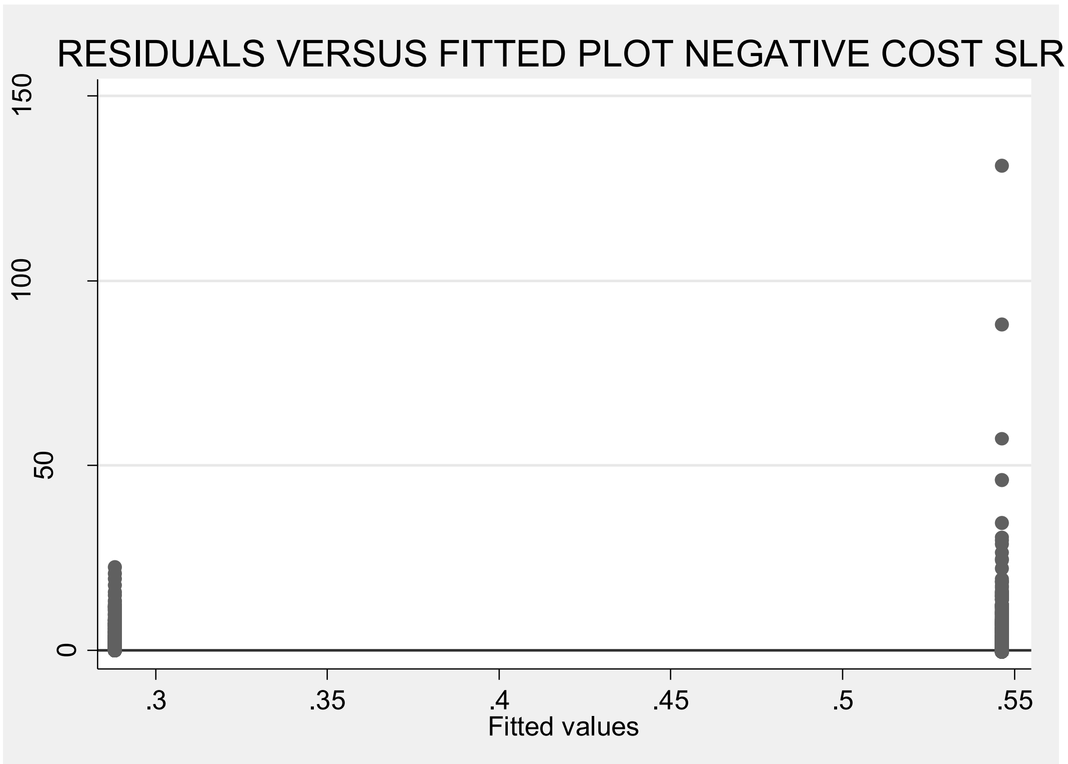
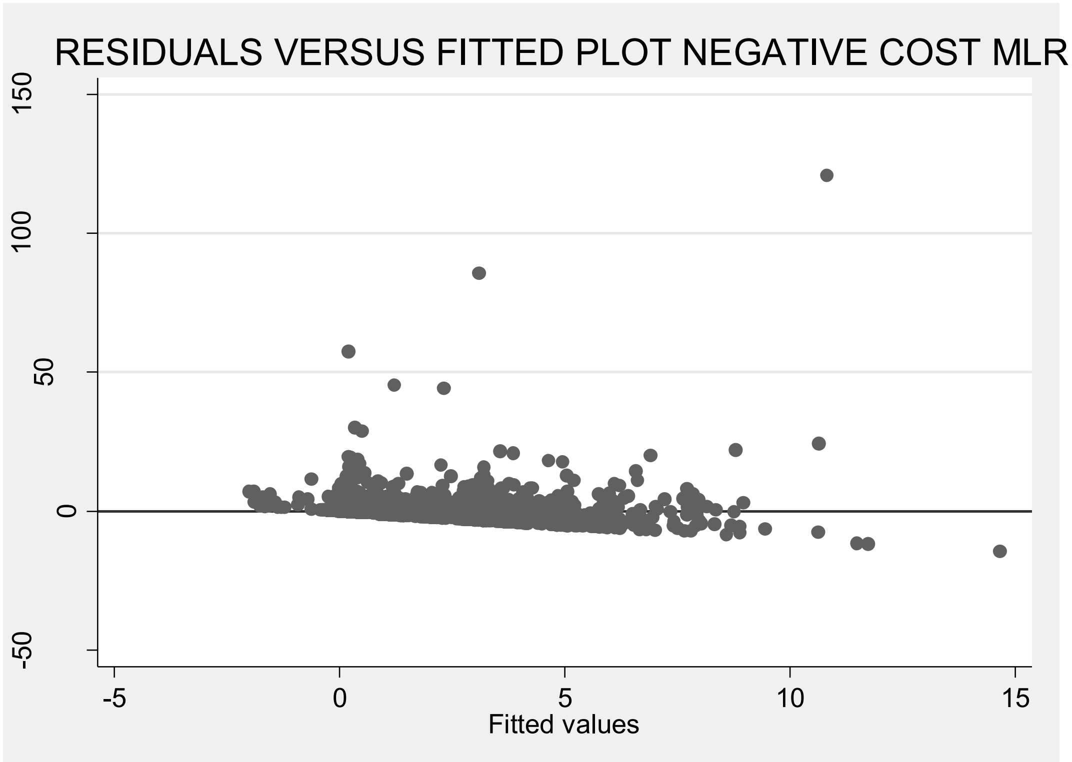


Figure 15. Residual plots for net-benefit regressions on negative cost (equivalent to net benefit when $\lambda = 0$) and effect (equivalent to net benefit when $\lambda \rightarrow \infty$) for each of the three models

a. Negative cost regression SLR



b. Negative cost regression multiple linear regression



c. Negative cost regression multiple linear regression with interaction terms

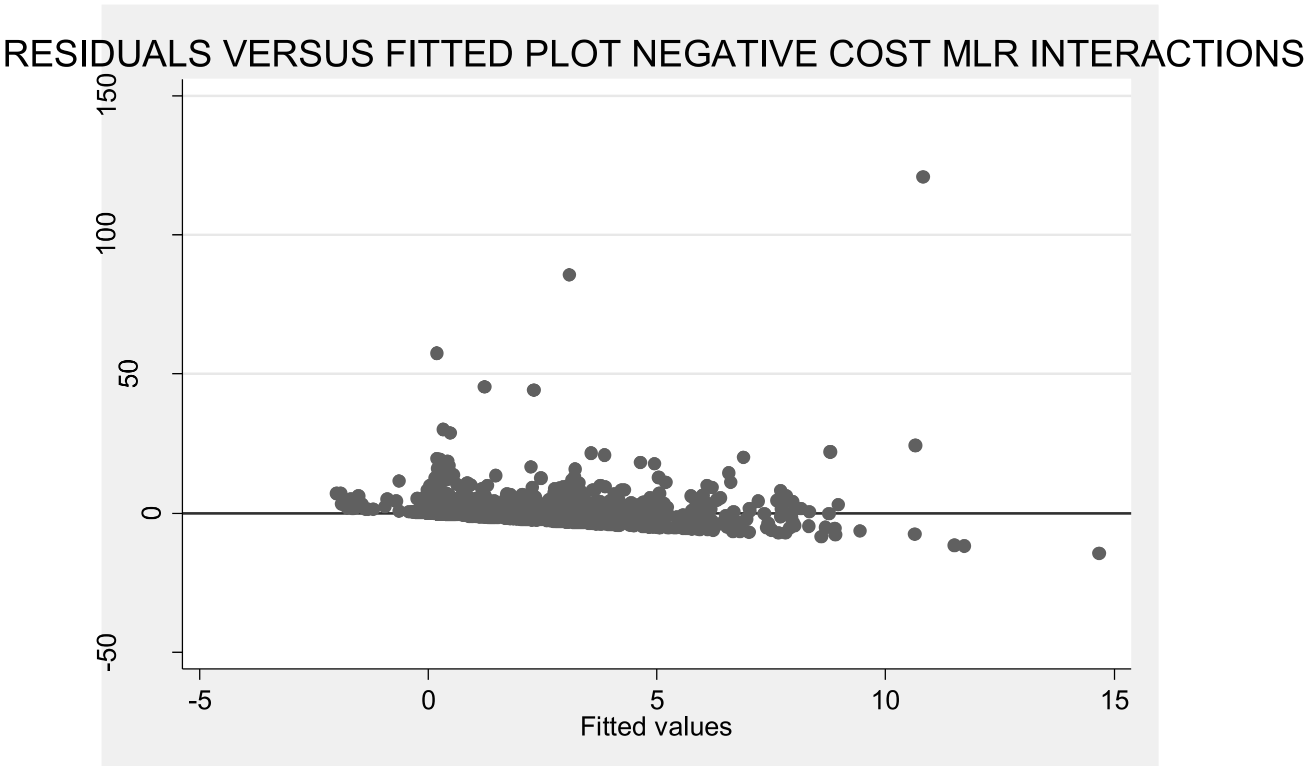


Figure 16. Cost-effectiveness acceptability curve: GLM Gamma with log link (unadjusted)

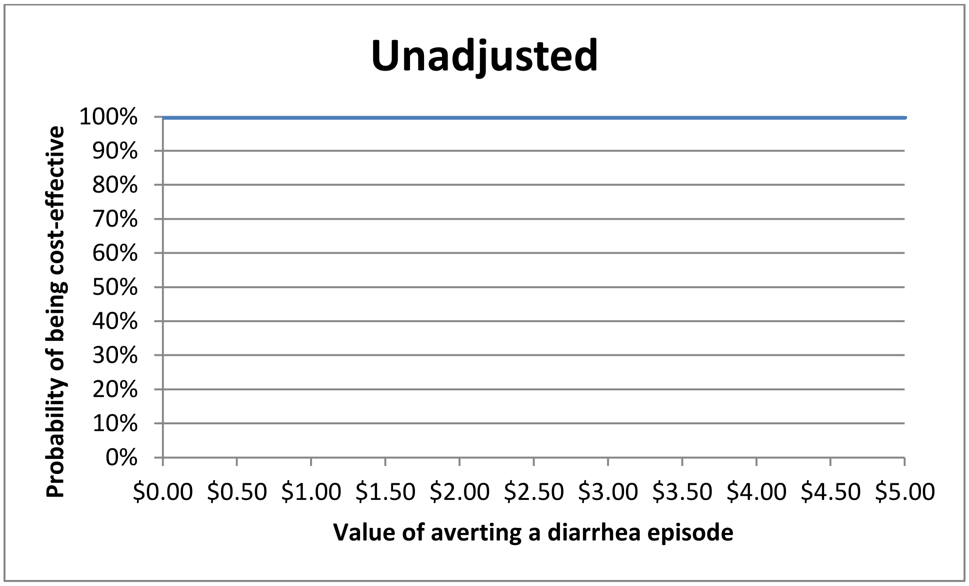


Figure 17. Cost-effectiveness acceptability curves: GLM Gamma with log link (adjusted)

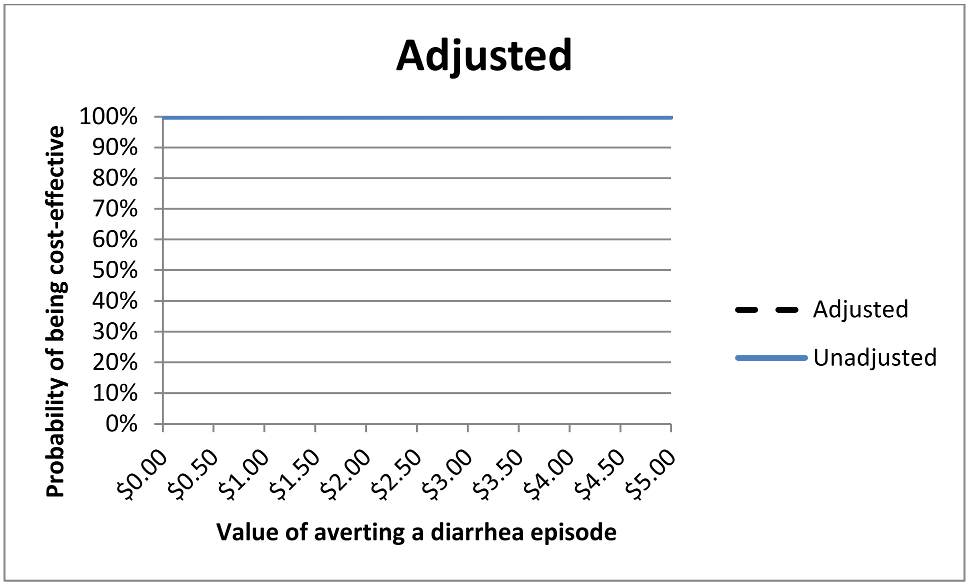
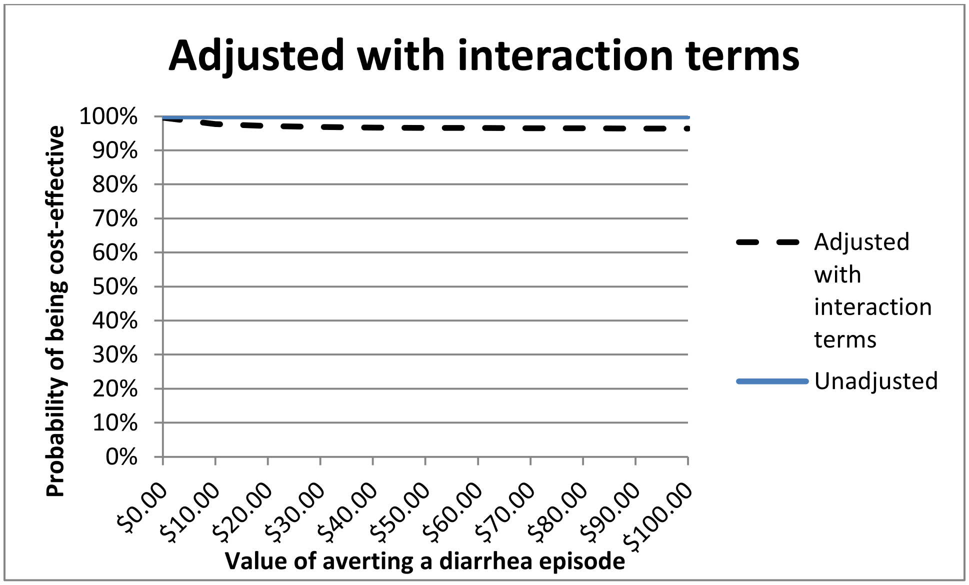


Figure 18. Cost-effectiveness acceptability curve: GLM Gamma with log link – fully interacted



11.4 Paper 3

Table 25. Attributes of each health provider considered in cost-effectiveness analysis of bundled diarrhea and pneumonia interventions

a) Community health worker

	Population ratio of health workers	Total per district/village	Target population	Proposed scope of work (interventions)	Percent delivered through channel	Core products distributed	Minutes	% time by activity
			Children 6-59 months	Vitamin A	50%	Vitamin A capsules	6	13%
ASHA	1/1068	2	Children 0-59 months	ORS	50%	ORS sachets	10	22%
AWW	1/1000	2	Children 0-59 months	Zinc treatment of uncomplicated diarrhea	70%	Zinc tablets	10	22%
			Children 1-59 months	Oral antibiotics for case management of pneumonia in children	50%	Antibiotic capsules	20	43%

b) Outreach

	Population ratio of health workers	Total per district/ village	Target population	Proposed scope of work (interventions)	Percent delivered through channel	Core products distributed	Minutes	% time by activity
Outreach workers			Births	Breastfeeding promotion	50%	None	70	92%
			Children 6-59 months	Vitamin A	50%	Vitamin A capsules	6	8%

c) Nurses

	Population ratio of health workers	Total per district/ village	Target population	Proposed scope of work (interventions)	Percent delivered through channel	Core products distributed	Minutes	% time by activity
Nurses	17/10000 (2011)	4						
	1/1264	2	Births	Breastfeeding promotion	50%	None	70	30%
	1.73 / 10,000 (qualified practitioners), 4.9 / 10,000 census	1	Children 0-59 months	ORS	50%	ORS sachets	10	4%
			Children 0-59 months	Zinc treatment of uncomplicated diarrhea	30%	Zinc tablets	10	4%
			Births	Rotavirus vaccine	100%	Rotavirus vaccines	6	3%
			Births	HiB vaccine	100%	HiB vaccines	6	3%
			Births	Pneumococcal conjugate	100%	Pneumococcal vaccines	6	3%
			Children 1-59 months	Antibiotics for dysentery	100%	Antibiotic capsules	4	2%
			Children 0-59 months	Oral antibiotics for case management of pneumonia in children	50%	Antibiotic capsules	15	6%
			Children 0-59 months	Treatment of severe diarrhea	100%	IV kit, electrolyte solution, syringe, needle, cotton, take home materials with advice on preventing diarrhea at home	20	8%
			Children 0-59 months	Treatment of severe pneumonia	100%	Ampicillin, gentamycin, oxygen, pediatric nasogastric tubes, salbutamol, steroids	90	38%

d) Doctor

Population ratio of health workers	Total per district/ village	Target population	Proposed scope of work (interventions)	Percent delivered through channel	Core products distributed	Minutes	% time by activity
2.6 / 10,000	1	Children 0-59 months	Treatment of severe diarrhea	100%	IV kit, electrolyte solution, syringe, needle, cotton, take home materials with advice on preventing diarrhea at home	30	38%
6 / 10,000	2	Children 0-59 months	Treatment of severe pneumonia	100%	Ampicillin, gentamycin, oxygen, pediatric nasogastric tubes, salbutamol, steroids	50	63%
3.8 / 10,000 (qualified practitioners), 6.07 / 10,000 census	1						
5.1 / 10,000	1						

Table 26. Input parameters and distributions for cost-effectiveness analysis of bundled diarrhea and pneumonia interventions

	Triangular distribution			Gamma		
	Best estimate	Low	High	α	β	Source
Gamma distributions						
Antibiotics						
Ciprofloxacin (250mg tablet)	\$0.03	\$0.01	\$0.06	15.16	0.00	MSH
Amoxicillin	\$0.02	\$0.01	\$0.03	59.54	0.00	MSH
Ampicillin	\$0.15	\$0.09	\$0.38	11.41	0.02	MSH
Gentamycin	\$0.06	\$0.04	\$0.15	12.99	0.01	MSH
Dicloxicillin	\$0.04	\$0.03	\$0.07	28.40	0.00	MSH
Other drugs						
Vitamin A 100,000 dose	\$0.03	\$0.02	\$0.03	277.17	0.00	MSH
Vitamin A 200,000 dose	\$0.03	\$0.03	\$0.04	347.99	0.00	MSH
ORS sachets	\$0.10	\$0.09	\$0.13	154.38	0.00	MSH
20 mg zinc tablet	\$0.03	\$0.02	\$0.06	31.05	0.00	MSH
Salbutamol - tablets	\$0.00	\$0.00	\$0.01	14.96	0.00	MSH
Salbutamol - liquid	\$0.24	\$0.08	\$0.35	15.23	0.01	MSH
Oral prednisone	\$0.01	\$0.01	\$0.01	14.96	0.00	MSH
Paracetamol	\$0.002	\$0.001	\$0.003	25.41	0.00	MSH
Oxygen	\$3.70	\$0.99	\$6.41	11.19	0.33	Madsen et al (2009) (418)
X-ray	\$6.13	\$4.64	\$7.61	101.96	0.06	Madsen et al (2009) (418)
Inpatient stay	\$11.78	\$11.01	\$12.55	1410.10	0.01	Patel et al (2013) (85)
Vaccines						
Rotavirus	\$2.50	\$1.66	\$5.00	18.53	0.16	UNICEF, Verguet et al (2013) (167)
Hib	\$2.23	\$1.82	\$3.90	34.61	0.08	UNICEF
Pneumococcal conjugate	\$2.00	\$0.23	\$3.50	8.13	0.23	GAVI, (168), Verma et al (2012) (419)

	Triangular distribution			Gamma		
	Best estimate	Low	High	α	β	Source
Materials						
IV kits	$2.21	$2.07	$2.90	174.08	0.01	Amazon, Boundtree
Pediatric nasogastric tubes	$3.00	$1.53	$3.21	47.66	0.05	Vitality medical, Boundtree
electrolyte solution	$0.33	$0.01	$2.17	3.09	0.27	Patel et al (2013) (85)
syringe	$0.03	$0.01	$0.05	13.50	0.00	Alibaba
needle	$0.01	$0.00	$0.02	7.60	0.00	Alibaba
cotton	$0.01	$0.00	$0.02	7.60	0.00	Assumption
Safety box	$21.97	$14.96	$28.98	7.60	0.00	UNICEF
Salaries						
Auxiliary nurse midwife	$3,975	$3,701	$4,248	1264.12	3.14	Provider assessment survey
Medical officer	$8,452	$7,003	$9,902	203.95	41.44	Provider assessment survey
ASHA	$240	$228	$251	2518.59	0.10	Provider assessment survey
AWW	$240	$228	$251	2518.59	0.10	Provider assessment survey
	Triangular distribution			Beta		
Beta distributions	Best estimate	Low	High	α	β	
Diarrhea episodes per year	2.9	2.3	3.4	162.55	0.02	Fischer Walker et al (2012) (8)
Pneumonia Incidence	0.28	0.21	0.78	8.42	144.59	Rudan et al (2004) (420)
Wastage rates, pneumococcal vaccine, single dose	5.5%	1.0%	10.0%	5.84	35.90	Parmar et al (2010) (421)
Wastage rates, pneumococcal vaccine, two dose	14.0%	1.0%	27.0%	6.33	20.03	Parmar et al (2010) (421)
Wastage rates, pneumococcal vaccine, ten dose	24.0%	4.0%	44.0%	14.82	30.09	Parmar et al (2010) (421)
Wastage rate, HiB vaccine	33.0%	16.0 %	50.0%	13.07	422.44	Noaves et al (2011) (422)
Cloxacillin for breastfeeding mothers	3.0%	1.0%	5.0%	0.00	0.00	OneHealth

Table 27. Assumptions behind each intervention considered in cost-effectiveness analysis of bundled diarrhea and pneumonia interventions

Interventions	Drugs or components	Dose	Wastage	Human resources	Assumptions	Source
Vitamin A supplementation	Vitamin A capsules	6-11 months: 100,000 IU 12-59 months: 200,000 IU	5%	3 visits * 2 minutes CHW time 3 visits * 2 minutes nurse time	1) Often delivered through national campaigns (previously stand alone, but increasingly child health day) 2) The intervention is delivered while the child is seeing the health provider for some other reason	(423), (424)
Oral rehydration solution	Sachets containing sodium chloride, potassium bicarbonate, glucose	3 sachets (One Health) (DAZT used two sachets)	0%	1 visit * 10 minutes CHW time 1 visit * 10 minutes nurse time	Based on WHO CHCET model 80% mild diarrhea 20% some dehydration	One Health assumes 3 sachets DAZT used two sachets ORASEL used 2 sachets

Breastfeeding promotion	 Cloxacillin for mastitis	6 counselling sessions 14 days, 4 doses per day	0% 0%	70 minutes CHW time 70 minutes nurse time	1) Two antenatal sessions, one immediately after birth, one first week after birth, one at six weeks, one between 5-6 months of life 2) No additional training was assumed as breastfeeding counselling is already part of ASHA responsibilities 3) 1-5% of breastfeeding mothers will develop mastitis	(323), (424)
Rotavirus vaccine	Two new oral rotavirus vaccines (Rotarix, Rotateq)	2 doses	5%	3 visits * 2 minutes nurse time	1) 5% wastage based on national wastage rates for most countries (425) 2) Cold chain costed separately 3) No sharps management necessary since oral vaccine	(426), (424)
Antibiotics for dysentery	Ciprofloxacin (250mg)	2 tablets per day, 3 days	0%	2 visits * 2 minutes nurse time	1) 1.7-2.78 episodes per year 2) 5% of episodes have dysentery	(427), (424)
Zinc supplementation (treatment)	Dispersible zinc tablets (20mg for children 6-59 months, 10mg for children 0-6 months)	14 days	0%	2 visits * 5 minutes CHW time 2 visits * 5 minutes nurse time	1) 1.7-2.78 episodes per year 2) 99% mild to moderate	(41), (424)
Treatment of severe diarrhea	ORS, IV kit, Electrolyte solution, syringe, needle, cotton, take home materials with advice on	5 days ORS	0%	10 minute diagnosis 3 inpatient days in a general ward (doctor 3 days x 10 minutes, nurse 3 days x 20 minutes)	1) 1% of diarrhea cases will require treatment for severe diarrhea (DAZT data are consistent with 1%, no assumption stated in OneHealth)	(271), (428), (424)

	preventing diarrhea at home				2) 100% of cases will receive treatment	
Pneumococcal vaccine	Prequalified liquid plus delivery system + autodisposible syringe (0.5 ml) with needle and safety box for used syringes	2 primary doses with a booster	1%-10% for a single dose vial	3 visits * 2 minutes of doctor or nurse's time		(429), (424)
HiB vaccine	Reconstitution needle + autodisposible syringe (0.5ml), with needle, safety box used for syringes	3 doses	16%-50%	3 visits * 2 minutes of doctor or nurse's time		(430), (424)
Antibiotics for treatment and management of pneumonia	Oral amoxicillin (250mg) Paracetamol Salbutamol	3 days amoxicillin * twice daily 6 doses (average) 4 days salbutamol (one 2mg tablet for infants 2-11 months, one 2mg tablet 3 times per day for children 1-5 years)	0%	CHW - 3 visits (10 minute initial visit and 5 minutes for each follow up) Clinic nurse - 2 visits (10 minute initial visit and 5 minutes for follow up)	50% of children are brought to facilities for care Salbutamol for wheezing for 10% of cases	(427), (424)

Treatment of severe pneumonia	Average five days hospitalization Injectable antibiotics (penicillin or ampicillin) Oxygen (100% children) Nebulized salbutamol (50% of wheezing children) 5% of children with bronchial asthma will require treatment with steroids for 4 days Chest x-ray 5 days outpatient care	-Ampicillin (50mg/kg IM every 6 hours for 5 days) -Gentamycin (7.5mg/kg IM once a day for 5 days) -Oxygen (1-2L/minute administered with nasal prongs for about 3 days) -Pediatric nasogastric tubes for children who cannot drink (20% of very severe cases for 3 days) -Salbutamol (2.5mg/4 times per day/5 days) -Prednisolone (1mg/kg for 3 days) After discharge: -Oral amoxicillin (15mg/kg 3 times/day for 5 days) -Hospital days: 5 days inpatient, 5 days outpatient	0%	Hospital: Nurse (1x10 minute, 6x5 minute per day) Medical doctor 10 minutes / day Outpatient follow up: Nurse 10 minutes per day	1) Standard management of very severe acute respiratory infections at the referral level 2) 2-3% of pneumonia cases will require treatment for severe pneumonia	(428), (424)

Table 28. Excluded studies from league table analysis of the cost-effectiveness of diarrhea and pneumonia interventions

Intervention	Reason for exclusion from league table
Breastfeeding promotion – effect on pneumonia	One study was available, although did not present costs disaggregated from the ICER. Lack of detail about implementation context (431)
Daily, weekly, and intermittent preventive zinc supplementation	These scenarios were presented by Brown et al (2013) (125); however, it was assumed that zinc supplementation is not feasible given difficulties India is having in scaling up zinc.
Zinc supplementation (preventive)	Did not present costs disaggregated from the ICER. Lack of detail about implementation context (431)
Rotavirus vaccination	Disaggregated costs not presented. Lack of detail about implementation context (432).
Measles vaccine	One study evaluating measles vaccine in India (324) was not included as deaths averted by the measles vaccine are attributed to measles and not diarrhea (90).
HiB vaccine	A study from Haryana State was found (329), but excluded due to more direct evidence from Gujarat (166)
Oral rehydration salts	Studies evaluate zinc treatment and ORS jointly (70)
Complementary feeding education	No economic evaluation exists
Complementary feeding education and supplements	No economic evaluation exists
Antibiotics for dysentery	No economic evaluation exists
Vitamin A supplementation	No economic evaluation exists
Antibiotics for treating and managing pneumonia	No economic evaluation exists

Table 29. League table evaluation of the cost-effectiveness of interventions to address diarrhea and pneumonia

Intervention	Setting	Cost/DALY averted	Budget	Source
Zinc supplementation (treatment)	India	$46	$2,968,203	Lefevre et al (forthcoming) (70)
Rotavirus immunization	India	$66	$730,901	Verguet et al (2013) (167)
Pneumococcal conjugate vaccine	Countries eligible for GAVI - India is listed	$215	$1,995,958	Sinha et al (2007) (168)
HiB vaccine - Government + household costs - India, Gujarat	India, Gujarat	$612	$30,350,386	Clark et al (2013) (166)
Breastfeeding - Effect on diarrhea	South Asia (World Bank regions)	$1,615	$1,562,736	Keusch et al (2006) (4)

Table 30. Coverage values for diarrhea and pneumonia interventions considered in bundled cost-effectiveness analysis

	Conservative scale up					Universal coverage				
	2011	2012	2013	2014	2015	2011	2012	2013	2014	2015
Vitamin A supplementation	15.6%	29.7%	43.8%	57.9%	72.0%	15.6%	34.2%	52.8%	71.4%	90.0%
Oral rehydration solution	15.3%	27.5%	39.6%	51.8%	63.9%	15.3%	34.0%	52.7%	71.3%	90.0%
Exclusive breastfeeding										
0-1 mo	69.0%	69.3%	69.5%	69.8%	70.0%	69.0%	74.3%	79.5%	84.8%	90.0%
1-5 mo	27.6%	38.2%	48.8%	59.4%	70.0%	27.6%	43.2%	58.8%	74.4%	90.0%
Predominant breastfeeding										
0-1 mo	18.8%	16.6%	14.4%	12.2%	10.0%	18.8%	15.4%	11.9%	8.5%	5.0%
1-5 mo	32.0%	26.5%	21.0%	15.5%	10.0%	32.0%	25.3%	18.5%	11.8%	5.0%
Partial breastfeeding										
0-5 mo	9.5%	9.6%	9.8%	9.9%	10.0%	9.5%	7.1%	4.8%	2.4%	0.0%
12-23 mo	38.8%	31.6%	24.4%	17.2%	10.0%	38.8%	29.1%	19.4%	9.7%	0.0%
Any breastmilk										
6-11 mo	93.7%	93.7%	93.7%	93.7%	93.7%	93.7%	94.0%	94.4%	94.7%	95.0%
6-23 mo	82.3%	82.3%	82.3%	82.3%	82.3%	82.3%	83.0%	83.7%	84.3%	85.0%
Rotavirus vaccine	0.0%	18.0%	36.0%	54.0%	72.0%	0.0%	22.5%	45.0%	67.5%	90.0%
Antibiotics for dysentery	13.0%	23.0%	32.9%	42.9%	62.8%	13.0%	32.3%	51.5%	70.8%	90.0%
Zinc supplementation (treatment)	2.5%	7.5%	12.5%	17.4%	22.4%	2.5%	24.4%	46.3%	68.1%	90.0%
Treatment of severe diarrhea	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Antibiotics for treatment and management of pneumonia	11.7%	16.7%	21.7%	26.6%	31.6%	11.7%	31.3%	50.9%	70.4%	90.0%
Treatment of severe pneumonia	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Pneumococcal vaccine	0.0%	18.0%	36.0%	54.0%	72.0%	0.0%	24.0%	48.0%	72.0%	96.0%
HiB vaccine	0.0%	18.0%	36.0%	54.0%	72.0%	0.0%	24.0%	48.0%	72.0%	96.0%

Table 31. Additional cost per capita to achieve targeted coverage rates for conservative and universal scale up scenarios by 2015

a) Conservative coverage

Intervention	2011	2012	2013	2014	2015	Cost/year	Total 5-year	% allocation
Breastfeeding promotion	$1,022,725	$996,535	$971,002	$946,112	$921,847	$971,644	$4,858,221	10.05%
Antibiotics for treatment and management of pneumonia	$31,288	$43,293	$79,653	$113,858	$146,003	$82,819	$414,094	0.86%
Antibiotics for dysentery	$4,393	$7,530	$10,481	$13,253	$18,857	$10,903	$54,514	0.11%
Pneumococcal vaccine	$0	$370,991	$720,371	$1,049,083	$1,358,037	$699,696	$3,498,482	7.24%
Vitamin A supplementation	$151,641	$254,340	$350,927	$441,673	$526,834	$345,083	$1,725,415	3.57%
Oral rehydration solution	$3,140,658	$3,995,141	$4,797,184	$5,549,116	$6,253,177	$4,747,055	$23,735,277	49.11%
HiB vaccine	$0	$778,850	$1,512,330	$2,202,423	$2,851,033	$1,468,927	$7,344,636	15.20%
Rotavirus vaccine	$0	$259,901	$504,663	$734,946	$951,386	$490,179	$2,450,896	5.07%
Zinc supplementation (treatment)	$237,976	$690,824	$2,009,865	$3,251,483	$4,419,068	$2,121,843	$10,609,216	21.95%
Treatment of severe diarrhea	$18,178	$17,649	$17,135	$16,636	$16,151	$17,150	$85,748	0.18%
Treatment of severe pneumonia	$504,160	$489,476	$475,219	$461,378	$447,940	$475,635	$2,378,173	4.92%
Total	$4,052,614	$6,486,181	$9,667,323	$12,657,654	$15,465,589	$1,380,839	$48,329,361	100%

b) Universal coverage

Intervention	2011	2012	2013	2014	2015	Cost/year	Total 5-year	% allocation
Breastfeeding promotion	$1,022,725	$1,068,487	$1,110,715	$1,149,577	$1,107,347	$1,107,347	$5,536,736	8.80%
Antibiotics for treatment and management of pneumonia	$247,847	$643,218	$1,015,347	$1,365,253	$993,116	$993,116	$4,965,578	7.89%
Antibiotics for dysentery	$4,393	$10,582	$16,406	$21,881	$16,057	$16,057	$80,286	0.13%
Pneumococcal vaccine	$0	$583,854	$1,133,698	$1,651,017	$1,101,161	$1,101,161	$5,505,807	8.75%
Vitamin A supplementation	$151,641	$336,918	$511,273	$675,185	$500,827	$500,827	$2,504,133	3.98%
Oral rehydration solution	$1,519,741	$3,276,427	$4,929,492	$6,483,482	$4,830,382	$4,830,382	$24,151,910	38.37%
HiB vaccine	$0	$1,225,731	$2,380,061	$3,466,108	$2,311,754	$2,311,754	$11,558,771	18.36%
Rotavirus vaccine	$0	$409,025	$794,223	$1,156,636	$771,429	$771,429	$3,857,147	6.13%
Zinc supplementation (treatment)	$217,038	$2,054,481	$3,784,705	$5,412,397	$3,682,136	$3,682,136	$18,410,681	29.25%
Treatment of severe diarrhea	$18,178	$17,649	$17,135	$16,636	$17,150	$17,150	$85,748	0.14%
Treatment of severe pneumonia	$504,160	$489,476	$475,219	$461,378	$475,635	$475,635	$2,378,173	3.78%
Total	$2,410,758	$7,809,707	$12,892,108	$17,671,822	$1,798,473	$1,798,473	$62,946,563	100%

Table 32. Program costs per year for diarrhea and pneumonia interventions considered in bundled cost-effectiveness analysis

Component	Cost
Start up	$60,011
Facility	$48,206
Vehicles	$36,220
In service training	$3,340
Information, education, and communication campaign	$16,251
Cold chain	$476,870
Total	$640,899

Table 33. Incremental cost-effectiveness of individual diarrhea and pneumonia interventions

	Incremental cost		Deaths averted		DALYs averted		Individual Cost per death averted		Individual Cost per DALY averted	
Intervention	Cons*	Univ*	Cons	Univ	Cons	Univ	Cons	Univ	Cons	Univ
Breastfeeding promotion	-$42,614	$220,771	67	578	1,892	16,319	-$636	$382	-$23	$14
Antibiotics for treatment and management of pneumonia	$172,979	$1,504,331	1,007	1,512	28,432	42,690	$172	$995	$6	$35
Antibiotics for dysentery	$72,727	$80,894	174	201	4,913	5,675	$418	$402	$15	$14
Vitamin A supplementation	$433,456	$735,738	228	307	6,437	8,668	$1,901	$2,397	$67	$85
Pneumococcal vaccine	$1,416,300	$2,195,502	695	1,022	19,623	28,855	$2,038	$2,148	$72	$76
Oral rehydration solution	$3,170,782	$6,481,290	1,000	1,471	28,234	41,533	$3,171	$4,406	$112	$156
Rotavirus vaccine (Rotarix, Rotateq)	$1,009,650	$1,555,527	243	310	6,861	8,753	$4,155	$5,018	$147	$178
HiB vaccine	$2,909,296	$4,545,135	496	709	14,004	20,018	$5,866	$6,411	$208	$227
Zinc supplementation (treatment)	$4,239,356	$6,783,286	329	484	9,289	13,665	$12,886	$14,015	$456	$496
Treatment of severe diarrhea	$56,236	$56,236	0	0	0	0	N/A	N/A	N/A	N/A
Treatment of severe pneumonia	$2,043	$2,043	0	0	0	0	N/A	N/A	N/A	N/A

*Scenarios include conservative and universal

Table 34. Incremental cost-effectiveness of the overall package of diarrhea and pneumonia interventions

Cost effectiveness outputs	Conservative	95% confidence interval		Universal	95% confidence interval	
Incremental costs 3% discount	$12,053,874	$9,997,968	$14,255,424	$20,392,309	$16,941,682	$24,161,841
Incremental costs 0% discount	$15,688,116	$13,161,090	$18,413,050	$27,575,293	$23,165,933	$32,591,908
Incremental costs 6% discount	$11,497,091	$9,599,016	$13,525,660	$21,209,176	$17,834,292	$25,075,790
Deaths averted	2,754			4,004		
Cost/death averted	$4,376.86	$3,630.34	$5,176.26	$5,092.98	$4,231.19	$6,034.43
Cost/DALY (3,0) averted	$155.02	$128.58	$183.33	$180.38	$149.86	$213.73
Cost/DALY (3,1) averted	$138.59	$114.96	$163.91	$161.27	$133.98	$191.08
Cost/DALY (0,0) averted	$91.02	$76.36	$106.83	$110.04	$92.45	$130.06
Cost/DALY (6,0) averted	$279.17	$233.08	$328.42	$354.22	$297.85	$418.79

Table 35. Costs of packages of diarrhea and pneumonia interventions bundled according to service delivery channel

Intervention	Community			Outreach		
	Incremental	Cost / year	Total 5 year	Incremental	Cost / year	Total 5 year
Ambitious coverage						
Breastfeeding promotion	-$40,351	$388,658	$1,943,289	-$40,351	$38,866	$194,329
Antibiotics for treatment and management of pneumonia	$57,358	$41,409	$207,047			
Antibiotics for dysentery	$7,232	$5,451	$27,257			
Pneumococcal vaccine						
Vitamin A supplementation	$187,596	$172,542	$862,708	$187,596	$172,542	$862,708
Oral rehydration solution	$1,556,259	$2,373,528	$11,867,639			
HiB vaccine						
Rotavirus vaccine						
Zinc supplementation (treatment)	$2,926,765	$1,485,290	$7,426,451			
Treatment of severe diarrhea						
Treatment of severe pneumonia						
Totals	$4,694,859	$744,480	$22,334,390	$147,245	$105,704	$1,057,037
Universal coverage						
Vitamin A supplementation	$174,593	$553,674	$2,768,368	$174,593	$553,674	$2,768,368
Oral rehydration solution	$1,655,320	$496,558	$2,482,789			
Breastfeeding promotion	$33,849	$442,939	$2,214,694	$8,462	$1,606	$8,029
Rotavirus vaccine						
Antibiotics for dysentery	$11,664	$250,413	$1,252,067			
Zinc supplementation (treatment)	$3,465,099	$3,381,267	$16,906,337			
Treatment of severe diarrhea						
Pneumococcal vaccine						
HiB vaccine						
Antibiotics for treatment and management of pneumonia	$745,269	$8,575	$42,874			
Treatment of severe pneumonia						
Totals	$6,117,573	$887,351	$25,826,029	$193,648	$288,233	$2,829,363

Intervention	Clinic			Hospital		
	Incremental	Cost / year	Total 5 year	Incremental	Cost / year	Total 5 year
Ambitious coverage						
Breastfeeding promotion						
Antibiotics for treatment and management of pneumonia	-$50,439	$485,822	$2,429,111			
Antibiotics for dysentery	$57,358	$41,409	$207,047			
Pneumococcal vaccine	$7,232	$5,451	$27,257			
Vitamin A supplementation	$1,358,037	$699,696	$3,498,482			
Oral rehydration solution						
HiB vaccine	$1,556,259	$2,373,528	$11,867,639			
Rotavirus vaccine	$2,851,033	$1,468,927	$7,344,636			
Zinc supplementation (treatment)	$951,386	$490,179	$2,450,896			
Treatment of severe diarrhea	$1,254,328	$636,553	$3,182,765			
Treatment of severe pneumonia				-$1,873	$17,150	$85,748
Totals				-$68,361	$475,635	$2,378,173
Universal coverage	$7,985,193	$775,196	$31,007,831	-$70,235	$246,392	$2,463,921
Vitamin A supplementation						
Oral rehydration solution						
Breastfeeding promotion	$1,655,320	$496,558	$2,482,789			
Rotavirus vaccine	$42,311	$8,029	$40,143			
Antibiotics for dysentery	$771,429	$1,101,161	$5,505,807			
Zinc supplementation (treatment)	$5,832	$250,413	$1,252,067			
Treatment of severe diarrhea	$1,039,530	$1,449,115	$7,245,573			
Pneumococcal vaccine				-$1,873	$2,311,754	$11,558,771
HiB vaccine	$1,101,161	$771,429	$3,857,147			
Antibiotics for treatment and management of pneumonia	$2,311,754	$3,682,136	$18,410,681			
Treatment of severe pneumonia	$372,634	$8,575	$42,874			
Totals				-$68,361	$475,635	$2,378,173

Table 36. Cost-effectiveness of different packages of diarrhea and pneumonia interventions bundled according to service delivery channel

Community	Conservative	95% confidence interval		Universal	95% confidence interval	
Costs	$5,335,758	$4,246,165	$6,577,653	$9,729,797	$7,817,684	$11,969,200
Deaths averted	1,979			3,117		
Cost/death averted	$2,696	$2,146	$3,324	$3,122	$2,508	$3,840
Cost/DALY averted	$95.49	$75.99	$117.72	$110.56	$88.83	$136.00
Outreach						
Costs	$818,408	$772,617	$877,103	$1,006,480	$923,125	$1,113,916
Deaths averted	139			757		
Cost/death averted	$5,888	$5,558	$6,310	$1,330	$1,219	$1,471
Cost/DALY averted	$208.53	$196.87	$223.49	$47.09	$43.19	$52.12
Clinic						
Costs	$8,626,092	$7,450,238	$9,963,515	$14,849,268	$12,810,437	$17,084,648
Deaths averted	2,726			3,970		
Cost/death averted	$3,164	$2,733	$3,655	$3,740	$3,227	$4,303
Cost/DALY averted	$112.08	$96.80	$129.45	$132.48	$114.29	$152.42
Hospital						
Costs	$582,652	$544,903	$612,360	$625,025	$587,276	$612,360
Deaths averted	0					
Cost/death averted	undefined	undefined	undefined	undefined	undefined	undefined
Cost/DALY averted	undefined	undefined	undefined	undefined	undefined	undefined

Table 37. Health system of the six DAZT study districts of Gujarat

	Medical college	District hospital	Sub district hospital	PHCs	CHCs	Sub centers
Study districts						
Banas Kantha	0	1	1	77	16	422
Dohad	0	1	1	63	11	332
Panch Mahals	0	1	2	65	12	400
Patan	1	1	0	32	11	210
Sabar Kantha	0	1	1	63	20	413
Surendranagar	1	1	1	35	11	200
Total	**2**	**6**	**6**	**335**	**81**	**1977**
Average	**0.3**	**1.0**	**1.0**	**55.8**	**13.5**	**329.5**
Other districts						
Ahmedabad	2	1	0	42	10	236
Amreli	0	1	2	38	9	247
Anand	1	1	0	46	10	274
Bharuch	0	1	0	38	7	200
Bhavnagar	1	1	1	46	4	360
Dangs	0	1	0	9	1	47
Ghandinagar	0	1	1	24	7	171
Jamnagar	1	1	1	37	11	265
Junagadh	0	1	1	57	20	390
Kheda	0	1	1	50	12	332
Kutch	1	1	0	39	13	279
Mehsana	0	1	1	50	13	288
Narmada	0	1	0	22	4	134
Navsari	0	1	1	37	10	281
Porbandar	0	1	0	10	3	84
Rajkot	1	1	1	44	18	330
Surat	2	0	0	47	13	345
Tapi	NA	1	NA	30	5	228
Vadodara	2	1	0	79	16	465
Valsad	0	1	1	40	9	330
Grand total	**13**	**25**	**17**	**1120**	**276**	**7263**
Average	**0.5**	**1.0**	**0.7**	**43.1**	**10.6**	**279.3**
Source: Census of India 2001(438)						

Figure 20. Overview of the Indian health care sector (434)

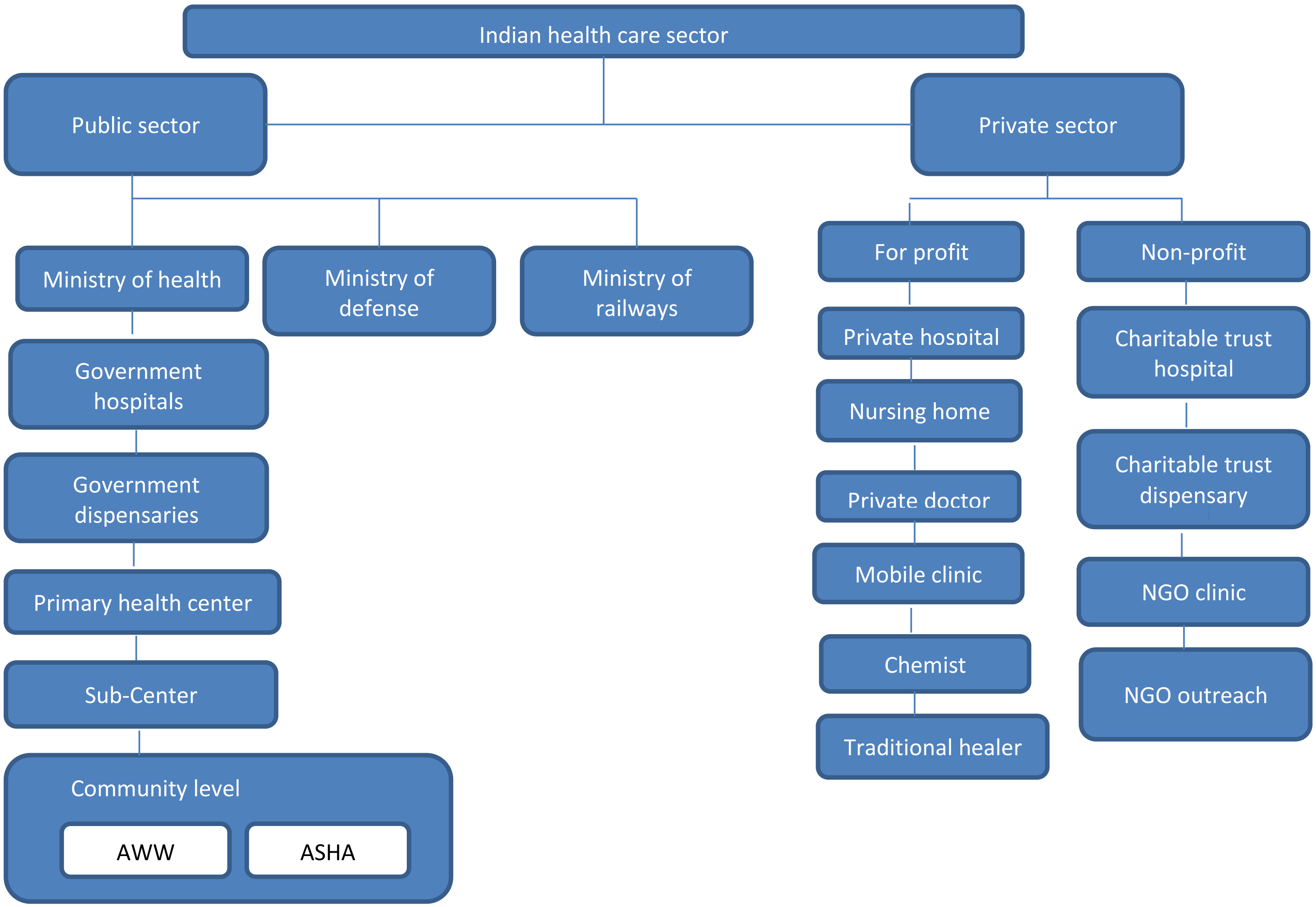
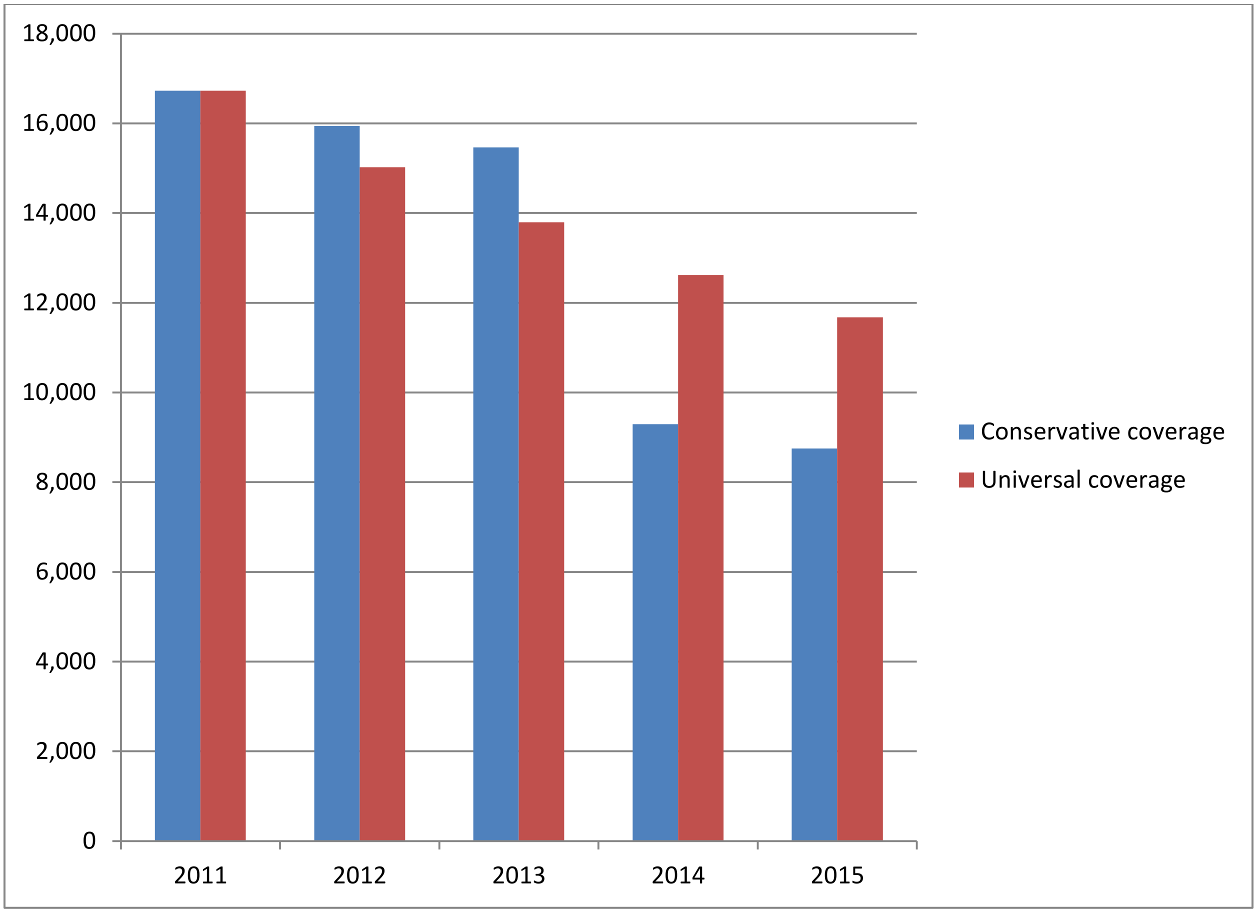
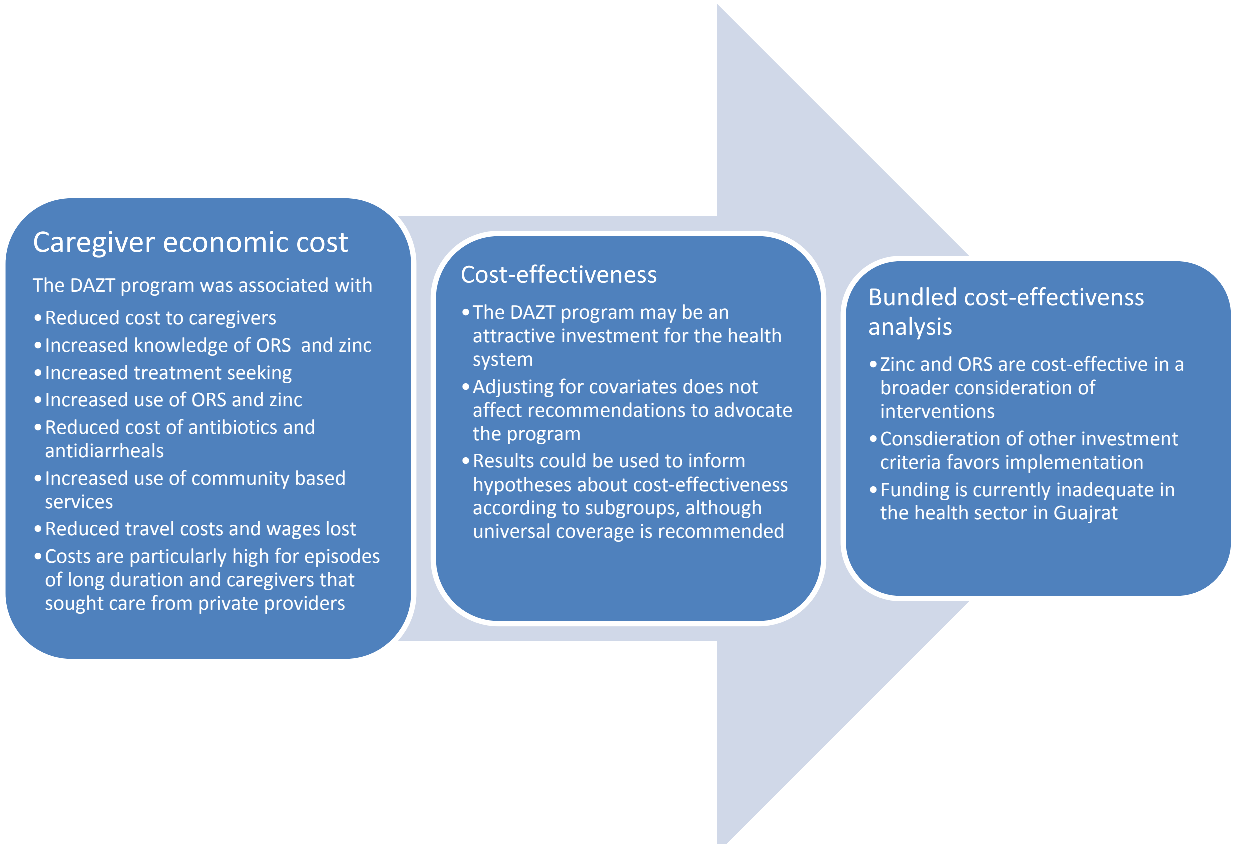


Figure 21. Total number of diarrhea and pneumonia deaths in six districts of Gujarat



11.5Policy chapter

Figure 22. Overview of main themes



12 Annex

12.1 Initial survey

BASELINE CROSS SECTIONAL SURVEY

Standard Codes (1= Yes; 2=No, 8= Does Not Know, 9=Not Applicable) **DATE_FILL**

Interviewer code ☐☐ **INT_CODE** Date of form f☐☐☐☐☐☐

PART A: ALL HOUSEHOLDS WITH AT LEAST 1 CHILD UNDER 5 YEARS OF AGE		
01.	Site code (3 = UP, 4 = Gujarat) **SITE_CODE**	☐
02.	Village name **VILL_NAME**	______________________
03.	Village Code **VILL_CODE**	☐☐
04.	Name of head of the household **NAME_HEAD**	______________________
05.	Phone number **PHONE**	☐☐☐☐☐☐☐☐☐☐
06.	Household **ID HH_ID**	☐☐☐☐
07.	Type of family (3 =Nuclear, 4=Joint) **TYPE_FAM**	☐
08.	How many people are living in this house? **NO_MEMB_M** **NO_MEMB_F** **NO_MEMB_MCH**	☐☐ Male (≥5 years) ☐☐ Female (≥5 years) ☐☐ Male child (< 5 years)

	NO_MEMB _FCH	Female child (< 5 years)
	Details of youngest child in the age category 2 to 59 months	
09.	Name of the child **CH_NAME**	____________________
10.	Age of the child (in completed years and months) **AGE_YR AGE_MO**	Years Months
11.	Sex (3=Male, 4=Female) **SEX**	
12.	Was the child breast-fed in the previous 24 hrs **CH_BF**	
13.	Name of the mother **MOTHER_NAM**	____________________
14.	Name of the father **FATHER_NAM**	____________________
CAREGIVER'S KNOWLEDGE ABOUT DIARRHEA MANAGEMENT		
15.	What types of symptoms associated with diarrhea would cause you to take the child to a doctor or health facility immediately **(Mark 1 for YES for those mentioned by the caregiver spontaneously and 2 for NO if not mentioned)**	
15.1.	Child has diarrhea for too many days **DIAR_DAY**	
15.2.	Child passes too many stools **NO_STOOL**	
15.3.	Child has watery stools **WAT_STOOL**	
15.4.	Dehydration (pani ki kami) **DEHYDRATION**	

15.5.	Child is lethargic **LETHARGIC**	☐
15.6.	Child not able to drink or breastfeed **NOT_DRINK**	☐
15.7.	Child becomes sicker **SICKER**	☐
15.8.	Child develops fever **FEVER**	☐
15.9.	Child has fast breathing **FAST_BREATH**	☐
15.10.	Child has difficulty breathing (Mushkil/pareshani **DIFF_BREATH**	☐
15.11.	Child passes blood in the stool **BLD_STL**	☐
15.12.	Child is drinking poorly or not as often **DRINK_POOR**	☐
15.13.	Child has sunken eyes **SUNK_EYE**	☐
15.14.	Child is irritable **IRRETABLE**	☐
15.15.	Child is weak **WEAK**	☐
15.16.	Child is vomiting **VOMITING**	☐
15.17.	Others, specify **OTH15_1, OTH15_SP1**	☐ ________
15.18.	**OTH15_2 , OTH15_SP2**	☐ ________
15.19.	**OTH15_3 , OTH15_SP3**	☐ ________

16.	What are the appropriate sources of care in your village or outside your village where a child with diarrhea can be taken for treatment **(Mark1 for YES if mentioned by the caregiver and 2 for NO if not mentioned)**	
16.1.	Primary health centre / Govt hospital / Govt dispensary **CARE_PHC**	☐
16.2.	Auxiliary nurse midwife (ANM)/sub centre **CARE_ANM**	☐
16.3.	Private doctor **CARE_PP**	☐
16.4.	Nursing home/Private hospitals **CARE_NUR**	☐
16.5.	Mobile clinic **CARE_MOBCLIN**	☐
16.6.	Anganwadi worker (AWW)/Aganwadi centre (AWC) **CARE_AWW**	☐
16.7.	Accredited social health activist (ASHA) **CARE_ASHA**	☐
16.8.	Chemist………… **CARE_CHEM**	☐
16.9.	Traditional healer………… **CARE_THEAL**	☐
16.10.	Charitable Hospital/NGO/Trust…… **CARE_NGO**	☐

16.11.	Others, specify _ **CARE_OTH16_1 , CARE_OTH16_SP1**	☐ ________
16.12.	______ **CARE_OTH16_2 , CARE_OTH16_SP2**	☐ ________
16.13.	_______ **CARE_OTH16_3 , CARE_OTH16_3**	☐ ________
17.	Have you heard of a product called Jeevan Raksha Ghol/ORS? Have you seen this product (show packets available commercially or through government channels) **HEARD_ORS**	☐
18.	**If Q17 is NO, has not heard or seen THEN fill questions 18.1 to 18.8 with 9** **If Q17 is YES, then ask:** What is the packet used for? (Mark YES if mentioned by the caregiver spontaneously and NO if not mentioned)	
18.1.	Diarrhea…………..**ORS_DIAR**	☐
18.2.	Dehydration………..**ORS_DEHY**	☐
18.3.	Summer…………..**ORS_SUMM**	☐
18.4.	Vomiting…………..**ORS_VOMIT**	☐
18.5.	Malnutrition………..**ORS_MALN**	☐
18.6.	Others, specify _**ORS_OTH18_1 , ORS_OTH18_SP1**	☐ ________
18.7.	**ORS_OTH18_2 , ORS_OTH18_SP2**	☐ ________
18.8.	**ORS_OTH18_3 , ORS_OTH18_SP3**	☐ ________

19.	Have you heard of Zinc? **HEARD_ZINC** Show the zinc tablet/syrup available commercially or through government channels and ask have you ever seen a tablet or syrup like these?	☐
20.	**If Q19 is NO, has not heard or seen THEN fill questions 20.1 to 20.18 with 9** **If Q19 is YES, then ask:** From where did you hear about this product? (Mark YES if mentioned by the caregiver spontaneously and NO if not mentioned)	
20.1.	Primary health centre/Govt hospital / Govt dispensary **ZINC_PHC**	☐
20.2.	Auxiliary nurse midwife (ANM)/sub centre…**ZINC_ANM**	☐
20.3.	Private doctor………**ZINC_PP**	☐
20.4.	Nursing home/Private hospital…**ZINC_NUR**	☐
20.5.	Mobile clinic……**ZINC_MOBCLIN**	☐
20.6.	Anganwadi worker (AWW)/Aganwadi centre (AWC) **ZINC_AWW**	☐
20.7.	Accredited social health activist (ASHA) **ZINC_ASHA**	☐
20.8.	Chemist………**ZINC_CHEM**	☐
20.9.	Traditional healer………**ZINC_THEAL**	☐
20.10.	Announcements………**ZINC_ANNOUN**	☐

20.11.	Radio.........ZINC_RADIO	☐	
20.12.	Poster / Wall paintings......ZINC_POSTER	☐	
20.13.	Pamphlets.........ZINC_PAMPH	☐	
20.14.	Television.........ZINC_TEL	☐	
20.15.	Neighbour / family member......ZINC_NEIGH	☐	
20.16.	Others, specify ZINC_OTH20_1 , ZINC_OTH20_SP1	☐	
20.17.	ZINC_OTH20_2 , ZINC_OTH20_SP2	☐	
20.18.	ZINC_OTH20_3 , ZINC_OTH20_SP3	☐	
21.	**If Q19 is NO, has not heard or seen THEN fill questions 21.1 to 21.7 with 9** **If Q19 is YES, then ask:** What is zinc used for (Mark YES if mentioned by the caregiver spontaneously and NO if not mentioned)		
21.1.	Diarrhea ....ZINC_DIAR	☐	
21.2.	Pneumonia ....ZINC_PNEU	☐	
21.3.	Tonic...........ZINC_TONIC	☐	
21.4.	Fertilizer ....ZINC_FERT	☐	
21.5.	Others, specify ZINC_OTH21_1 , ZINC_OTH21_SP1	☐	

21.6.	ZINC_OTH21_2 , ZINC_OTH21_SP2	
21.7.	ZINC_OTH21_3 , ZINC_OTH21_SP3	
22.	Was the child admitted to the hospital in the last 3 mo? CH_HOSP **If NO, fill 22.1, 22.2, 23 and 24 with 9's for each box**	
22.1.	If yes, then date of admission. If more than once, then most recent hospitalization…DT_ADM	DD MM YY
22.2.	Duration of stay………DUR_DAY , DUR_HRS	Days ꜔urs
23.	What was the reason for admission?	
23.1.	Pneumonia…………ADM_PNEU	
23.2.	Diarrhea / dehydration……ADM_DIAR	
23.3.	Fever…………ADM_FEV	
23.4.	Others, specify ADM_OTH23_1 , ADM_OTH23_SP1	
23.5.	ADM_OTH23_2 , ADM_OTH23_SP2	
23.6.	ADM_OTH23_3 , ADM_OTH23_SP3	
24.	What was the cost of the hospitalization? COST_HOSP	
25.	Has your child had any of the following in the past two weeks? [Prompt for each option]	Yes / No Number of days

25.1.	Cough……………**COUGH_2WK , COUGH_2WK_D**	
25.2.	Difficulty in breathing………**DBR_2WK , DBR_2WK_D**	
25.3.	Fast breathing……**FBR_2WK , FBR_2WK_D**	
25.4.	Fever………**FEV_2WK , FEV_2WK_D**	
25.5.	Chest indrawing………**CHEST_2WK , CHEST_2WK_D**	
25.6.	Wheezing………**WHEZ_2WK , WHEZ_2WK_D**	
26.	Did your child have diarrhea ($\geq$ 3 loose/watery stools in 24 hours)	
26.1.	In the previous 24 hours……**DIAR_P24H**	
26.2.	In the previous 2 weeks……**DIAR_P2WK**	
27.	If the child had diarrhea in the last 2 weeks, record for the most recent episode **(including the ongoing one),** record	
	Date of onset (could be earlier than the last 14 days) **DT_ONSET**	DD MM YY
27.1.	Did the child recover (The child does not have loose or watery stools for at least 72 hours)… **CH_RECOVER**	
27.2.	If yes, date of recovery……**DT_RECOVER**	DD MM YY

PART B: RECENT DIARRHEAL EPISODE MORBIDITY AND CARE SEEKING TO BE FILLED OUT IF THE CAREGIVER ANSWERED **YES** TO **QUESTION 26** If Q 26 = NO, then skip PART B and go to PART C		
28.	If the child had diarrhea in the last 14 days, ask the mother about each of the following and enter appropriate answer [Prompt for each option]	
28.1.	Did your child pass blood in the stool during this illness **BLD_ST_14D**	☐
28.2.	Did your child have fever with this diarrheal illness **FEV_14D**	☐
28.3.	Did your child have vomiting with this diarrheal illness **VOM_14D**	☐
28.4.	Was the child very thirsty during this illness **THIRST_14D**	☐
28.5.	Was the child lethargic or irritable **IRRI_14D**	☐
28.6.	Did your child have sunken eyes **SUNK_14D**	☐
28.7.	Did your child have dehydration (pani ki kami) **DEHY_14D**	☐
29.	What were the maximum number of loose or watery stools passed on any day during the illness **NO_LW_STL**	☐☐
30.	How much did the child drink during this illness? 11= None; 12 = Less than normal; 13=Same as normal; 14 =More than normal **DRINK_HOWMUCH**	☐☐

31.	Did you offer the child food and did the child eat during this illness? **FOOD_EAT** 11 = Didn't offer and didn't eat; 12 = Ate less than normal; 13 =Ate the same as normal; 14=Ate more than normal	
32.	Did you seek advice or treatment outside home? **SEEK_ADV**	
33.	**(If No to Q32, then fill questions 33.1 to 33.13 with 9)** **If yes for Q32, then ask:** From whom did you seek advice / treatment?	
33.1.	Primary health centre/Govt hospital/Govt dispensary **ADV_PHC**	
33.2.	Auxiliary nurse midwife ANM)/sub centre…**ADV_ANM**	
33.3.	Private doctor……**ADV_PP**	
33.4.	Nursing home/Private hospital….**ADV_NURH**	
33.5.	Mobile clinic……**ADV_MOBCLIN**	
33.6.	Anganwadi worker (AWW)/Aganwadi centre (AWC)**ADV_AWW**	
33.7.	Accredited social health activist (ASHA) **ADV_ASHA**	
33.8.	Chemist……**ADV_CHEM**	
33.9.	Traditional healer……**ADV_THEAL**	

33.10.	Charitable hospital/NGO/Trust…**ADV_NGO**	
33.11. 33.12. 33.13.	Others, specify **ADV_OTH33_1 , ADV_OTH33_SP1** **ADV_OTH33_2 , ADV_OTH33_SP2** **ADV_OTH33_3 , , ADV_OTH33_SP3**	☐ ____ ☐ ____ ☐ ____
34.	**(If No to Q32, then fill in 999) WAIT_CARE** **If yes for Q32, then ask:** How many hours after the start of diarrhea did you wait before seeking care?	☐☐☐
35.	**(If YES to Q32, then fill in 9)** **If No for Q32, then ask:** Why did you not seek care? (Yes if caregiver mentions the reason listed, No for all NOT mentioned)	
35.1.	Child recovered………**RECOVER_35**	☐
35.2.	Illness not severe………**NSEV_35**	☐
35.3.	Home treatment adequate……**HTREAT_35**	☐
35.4.	Already had medicines in the home…**MED_HOME35**	☐
35.5.	Source not available………**SOUR_NAV**	☐
35.6.	Source too far from home…**SOUR_FAR**	☐
35.7.	No transportation……**NO_TRANS**	☐

35.8.	Nobody to accompany…**NO_ACCOMP**	☐
35.9.	Good source not available at that time **NO_WOODSOUR**	☐
35.10.	Money not available at that time…**NO_MONEY**	☐
35.11.	No time to take the child to the source…**NO_TIME**	☐
35.12.	Medicines given by available source are ineffective **MED_INEFF**	☐
35.13.	Family did not support seeking care…**FAM_NSUPP**	☐
35.14.	Others, specify **OTH35_1 , OTH35_SP1**	☐ ________
35.15.	**OTH35_2 , OTH35_SP2**	☐ ________
35.16.	**OTH35_3 , OTH35_SP3**	☐ ________
36.	Was the child administered any syrup, tablet, injection or IV fluids to treat this episode of diarrhea? **ANY_SYP**	☐
37.	**If Q36 is NO, fill questions 37.1 to 37.12 with 9** **If Q36 is YES, then ask:** What did you give? (Yes to all mentioned / No if not mentioned) Do not prompt for each	
37.1.	Syrup, unknown……**SYP_UNK**	☐
37.2.	Tablet, unknown……**TAB_UNK**	☐
37.3.	Powder, unknown…**POW_UNK**	☐

37.4.	Injection known.........**INJ_KNOW**	☐
37.5.	Injection unknown.........**INJ_UNK**	☐
37.6.	Antibiotics, specify ......**ANTIBIO , ANTIBIO_SP**	☐ ____________
37.7.	Antidiarrheal, specify ...... **ANTIDIA , ANTIDIA_SP**	☐ ____________
37.8.	Zinc............ **ZINC**	☐
37.9.	IV Fluids......... **IV_FLUID**	☐
37.10.	Others, specify **OTH37_1 , OTH37_SP1**	☐ ____________
37.11.	**OTH37_2 , OTH37_SP2**	☐ ____________
37.12.	**OTH37_3 , OTH37_SP3 OTH37**	☐ ____________
38.	Was the child administered ORS during this diarrheal episode? SHOW PACKETS **ORS_38**	☐
39.	**If Q38 is NO, fill questions 39.1 to 39.13 with 9** **If Q38 is YES, then ask:** Where did you get these packets from? (Yes for all mentioned / No if not mentioned)	
39.1.	Primary health centre / Govt hospital / Govt dispensary **PHC_39**	☐
39.2.	Auxiliary nurse midwife (ANM/subcentred) **ANM_39**	☐
39.3.	Anganwadi worker (AWW)/Aganwadi centre (AWC) **AWW_39**	☐

39.4.	Accredited social health activist (ASHA) **ASHA_39**	☐
39.5.	Chemist…… **CHEM_39**	☐
39.6.	Nursing Home/Private hospital… **NURSE_39**	☐
39.7.	Kept at home……… **HOME_39**	☐
39.8.	From neighbor/relative…… **NEIGH_39**	☐
39.9.	Charitable Hospital/NGO/Trust…… **NGO_39**	☐
39.10.	Private doctor…… **PP_39**	☐
39.11.	Others, specify **OTH39_1 , OTH39_SP1**	☐ ____________
39.12.	**OTH39_2 , OTH39_SP2**	☐ ____________
39.13.	**OTH39_3 , OTH39_SP3**	☐ ____________
40.	**If Q38 is NO, fill box with 9** **INST_ORS** **If Q38 is YES, then ask:** Did the provider instruct you how to prepare ORS?	☐
41.	**If Q38 is NO, fill boxes with 99** **How was the ORS prepared? ORS_41** 11 = 1 liter sachet prepared entirely in 1 liter of water; 12 = 200 ml sachet prepared in 200 ml water; 13 = either 11 or 12; 14 = Other, specify____________**ORS41_SP**	☐☐ ____________

42.	**If Q38 is NO, fill box with 9** **ORS_FREE** **If Q38 is YES, then ask:** Were the packets given for free or did you buy? (3 = free; 4 = bought; 5= some free/some bought)	☐
43.	**If Q38 is NO, fill boxes with 99** **ORS_DAYUSE** **If Q38 is YES, then ask:** How many days did you use it for?	☐☐
44.	**If Q38 is NO, fill boxes with 99** **ORS_NOUSE** **If Q38 is YES, then ask:** How many packets did you use during the episode?	☐☐
45.	Did you give any home available fluids **HOME_FLUID**	☐
46.	Did you administer zinc tablet/syrup to your child during this episode? (SHOW THE ZINC PRODUCTS) **ZINC_TAB**	☐
47.	**If Q46 is NO, fill questions 47.1 to 47.13 with 9** **If Q46 is YES, then ask:** Where did you get zinc from (YES if mentioned, NO if not mentioned)	
47.1.	Primary health centre / Govt Hospital / Govt dispensary **PHC_47**	☐
47.2.	Auxiliary nurse midwife (ANM)/sub centre…**ANM_47**	☐
47.3.	Anganwadi worker (AWW)/Aganwadi centre (AWC) **AWW_47**	☐
47.4.	Accredited social health activist (ASHA)… **ASHA_47**	☐
47.5.	Chemist……**CHEM_47**	☐

47.6.	Nursing Home/Private hospital…**NURH_47**	☐
47.7.	From Neighbour/relative…**NEIGH_47**	☐
47.8.	Kept at home……**HOME_47**	☐
47.9.	Charitable hospital,/NGO/Trust …**NGO_47**	☐
47.10.	Private doctor………**PP_47**	☐
47.11.	Others, specify **OTH47_1 , OTH47_SP1**	☐ ____________________
47.12.	**OTH47_2 , OTH47_SP2**	☐ ____________________
47.13.	**OTH47_3 , OTH47_SP3**	☐ ____________________
48.	**If Q46 is NO, fill box with 9** **If Q46 is YES, then ask:** Did you receive instruction as to how to prepare /give the zinc **INST_ZINC**	☐
49.	**If Q46 is NO, fill box with 9** **If Q46 is YES, then ask:** Did you get zinc for free or buy?(3=free; 4=bought; 5=some free/some bought) **ZINC_FREE**	☐
50.	**If Q46 is NO, fill questions 50.1 to 50.2 with 99** **If Q46 is YES, then ask:** How many zinc did you receive / buy?	

50.1.	Bottles ....NO_BOTT	☐☐ bottles
50.2.	Tablets.........NO_TAB	☐☐ tablets
51.	**If Q46 is NO, leave line blank** **If Q46 is YES, then ask:** Do you have the product (s)? If so, can I see it? If not, can you identify the product(s) you used on the chart? *Record the name of the product* **NAME_PROD**	________ ________
52.	**If Q46 is NO, fill 99** **If Q46 is YES, then ask:** How many days did you use it for? (fill number of days till today. Fill 99 if not used) **DAY_USE**	☐☐
53.	**If Q46 is NO, fill box with 9** **STIL_ZINC** **If Q46 is YES, then ask:** Are you still giving the zinc	☐
54.	How much did you spend in the treatment of this episode (in Rs). Fill only those boxes that are applicable with amount spent. Fill 0000 in others. [Prompt for each]	
54.1.	Consultation (the fees paid to the source of care) **CONS_54**	☐☐☐☐
54.2.	Dispensing (include costs of medicines dispensed by the source)...... **DISP_54**	☐☐☐☐
54.3.	Purchase of drugs (cost incurred to purchase drugs from the chemist or other source)...... **DRUG_54**	☐☐☐☐
54.4.	Purchase of ORS (Cost paid for ORS packets)... **ORS_54**	☐☐☐☐

54.5.	Purchase of zinc (Cost paid for zinc tablets/syrup) **ZINC_54**	
54.6.	Special food purchased (fruits, juice etc.) **FOOD_54**	
54.7.	Transportation (round trip cost paid for taking to the source of care)……… **TRAN_54**	
54.8.	Admission/hospitalization cost…**HOSP_54**	
54.9.	Did you (or spouse) take time off from work due to this illness ………**OFF_54**	
54.10.	If yes, how much wages did you lose because of this absence from work……**WAGE_54**	
54.11.	Other costs, specify…**OTH54 , OTH54_SP**	
PART C: SES/HOUSEHOLD DATA (FOR ALL HOUSEHOLDS WITH CHILD UNDER 5. CAN BE ANSWERED BY CAREGIVER OR OTHER ADULT LIVING IN HOUSEHOLD IF NECESSARY)		
55.	What are the years of schooling of this child's father? **(Fill 00 if father has never been to school or completed less than 1 year of schooling) FATH_SCH**	
56.	What is the occupation of father or male caregiver? 11=government service, 12=private service, 13=daily wage earner, 14=self employed, 15=farming, 16=does not work, 17=other, specify, 99=not applicable), **FATH_OCC , FATH_OCC_SP**	
57.	Is the mother alive? **MO_ALIVE**	

58.	What is the age (in years) of mother (or primary care giver if mother has died)? **AGE_MOTH**	
59.	What are the years of schooling of this child's mother (or primary caregiver if mother has died)? **MOTH_SCH** **(Fill 00 if mother has never been to school or completed less than 1 year of schooling)**	
60.	What is the occupation of mother/female caregiver? (11=government service, 12=private service, 13=daily wage earner, 14=self employed, 15=farming, 16=does not work, 17=other, specify, 99=not applicable), **MOTH_OCC , MOTH_OCC_SP**	
61.	What are the sources of drinking water used by your family? Prompt for each option.	
61.1.	Piped water into dwelling/yard/plot…**PIPED**	
61.2.	Public tap/standpipe….…**PUB_TAB**	
61.3.	Tube well or bore well………**TUBEWEL**	

61.4.	Hand pump…….**HAND_PUMP**	
61.5.	Dug well (covered/open)…… **DUGWEL**	☐
61.6.	Tanker truck………**TANKER**	☐
61.7.	ATM water machine……**ATM_WAT**	☐
61.8.	Surface water (River/Dam/Lake/Ponds/Stream/Canal/ Irrigation channel/shallow well)…… **SUR_WAT**	☐
61.9.	Others, specify **OTH61_1 , OTH61_SP1**	☐ ____________________
61.10.	**OTH61_2 , OTH61_SP2**	☐ ____________________
61.11.	**OTH61_3 , OTH61_SP3**	☐ ____________________
62.	Do you purify drinking water **PURIFY_WAT**	☐
63.	How much time does it take to obtain drinking water (round trip)? **TIME_OBTWAT** 3 = Water on premises; 4= Less than 30 minutes; 5=More than 30 minutes; 8= Don't know	☐
64.	Is electricity available in your house **ELECT_AV**	☐
65.	If the house has electricity, for an average of how many hours per day does it work? (99 if NO to question 64) **ELECT_HRS**	☐☐ Hours

66.	What are the common places of defecation of the household members? Prompt for each option.	
66.1.	Flush/pour flush to piped sewer system, or septic tank **SEWER**	☐
66.2.	Pit latrine with slab……**PIT_SLAB**	☐
66.3.	Pit latrine without slab/open pit…**PIT_WSLAB**	☐
66.4.	No facility/open space/field…**OPEN_SPACE**	☐
66.5.	Others, specify **OTH66_1 , OTH66_SP1**	☐ ________________
66.6.	**OTH66_2 , OTH66_SP2**	☐ ________________
66.7.	**OTH66_3 , OTH66_SP3**	☐ ________________
67.	If answer to Q66 if no facility/open space/field, fill 9 in options of Q67 Is the toilet facility for this household only or shared?	
67.1.	This household only……**ONLY_HOUSE**	☐
67.2.	Shared………**SHARED_67**	☐

68.	Do you possess a BPL card? **BPLCARD**	
69.	Do you possess an Antodaya /Annapurna card? **ANM_CARD**	
70.	What is the religion of father or head of the household? 11=Hindu; 12=Muslim; 13=Sikh; 14=Christian, 15=Others, specify________......**RELIGION , RELIGION_SP**	
71.	What is the ethnic group (caste/tribe) of father or head of household (3=Scheduled Caste, 4= Scheduled Tribe, 5=Other backward castes, 6= Other, specify) **ETHNIC , ETHNIC_SP**	____________________
72.	Does the house have (YES/NO) (observe where possible)	
72.1.	Radio or transistor……**RADIO**	
72.2.	Mattress………..**MATTRESS**	
72.3.	Pressure cooker……**COOKER**	
72.4.	Chair…………..**CHAIR**	

72.5.	Cot or bed...........**COT**	
72.6.	Television (TV), black and white......**TV_BW**	☐
72.7.	Television (TV), color......**TV_COL**	☐
72.8.	Refrigerator (FRIDGE)......... **FRIDGE**	☐
72.9.	Mobile Phone (Cell)...... **MOBILE**	☐
72.10.	Any other type of telephone......**LANDLINE**	☐
72.11.	Computer.........**COMPUTER**	☐
72.12.	Electric fan......**FAN**	☐
72.13.	Sewing machine......**SEW_MACH**	☐
72.14.	Watch / clock...........**WATCH**	☐
72.15.	Table..............**TABLE_72**	☐
72.16.	Tractor.........**TRACTOR**	☐
72.17.	Thresher......**THRESHER**	☐
72.18.	Water pump..............**WPUMP**	☐
72.19.	Motorcycle or scooter.........**SCOOTER**	☐
72.20.	Bicycle..............**BICYCLE**	☐

☐

☐

☐

72.21.	Animal drawn cart………**ANI_CART**	
72.22.	Car…………**CAR**	
72.23.	Farm animals of any kind……**F_ANIMAL**	☐
73.	Does the family own the house or any other house? [1=Yes (own), 2=No (rented)] **OWN_HOUS**	☐
74.	Does this household own any agricultural land? **AGRI_LAND**	☐
75.	How much agricultural land does the household own? **Fill 9999 if Q74 is NO** **LAND_AREA**	☐☐☐☐ Bigha
76.	Out of the land, how much is irrigated **Fill 9999 if Q74 is NO** **LAND_IRRI**	☐☐☐☐ Bigha
77.	Does the household have a bank account? **BANK_ACT**	☐
78.	Is the child covered by a health insurance scheme? INSERT LOCAL NAME FOR THIS. HAVE CAREGIVER SHOW CARD **HEALTH_SCHEME**	☐
79.	How many rooms TOTAL does this household have? **ROOMS**	☐☐
80.	How many rooms for SLEEPING does this household have? **ROOM_SLEEP**	☐☐
81.	**Record observations for ROOF MATERIAL** 11= No roof, 12=Thatch/palm leaf/reed/grass, 13= Mud, 14=	☐☐

	Sod/mud and grass mixture, 15= Plastic/polythene sheeting, 16= Rustic mat, 17= Palm/bamboo, 18= Raw wood planks/timber, 19= Unburnt brick, 20= Loosely packed stone, 21= Metal, 22= Wood, 23= Calamine/ cement/concrete, 24= Asbestos sheets, 25=Reinforced cement concrete (RCC) / cement/concrete, 26= Roofing shingles, 27= Tiles, 28=Slate, 29=others…**TYPE_ROOF , ROOF_SP**	
82.	**Record observations for EXTERIOR WALLS**	
	11= No walls, 12= Cane/palm/trunks/ bamboo, 13= Mud, 14=Grass/reeds/ thatch, 15= Bamboo with mud, 16= Stone with mud, 17= Plywood, 18= Cardboard, 19= Unburnt brick, 20= Raw wood/reused wood, 21= Cement/concrete, 22= Stone with lime/cement, 23= Burnt bricks, 24= Cement blocks, 25= Wood planks/ shingles, 26= Metal/ asbestos sheets, 27=Other…**TYPE_WALL , WALL_SP**	☐☐ ________
83.	**Record observations for MAIN FLOOR MATERIAL** 11= Mud/clay/earth, 12= Sand, 13= Dung, 14= Raw wood planks, 15= Palm/bamboo, 16= Brick, 17= Stone, 18= Paraquet or polished wood, 19= Vinyl or asphalt, 20= Ceramic tiles, 21=Cement, 22=Carpet, 23=Polished stone/marble/granite, 24=other) (observe whenever possible……**TYPE_FLOOR , FLOOR_SP**	☐☐ ________

END OF SURVEY. THANK CAREGIVER FOR PARTICIPATION

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Employment

Johns Hopkins Bloomberg School of Public Health, Department of International Health, Baltimore, MD

Sep 2013 –

Research Assistant

- **Economic evaluation of the costs and cost-effectiveness of the Diarrhea Alleviation through Zinc and oral rehydration therapy program at scale in Gujarat India**

Feb 2008 – Aug 2010

Senior Research Assistant

Cost-effectiveness analysis of interventions to prevent neonatal death Evaluations of community health worker programs in Pakistan and Bangladesh; and emollient treatment in a tertiary hospital in Bangladesh

Expected value of further information analysis evaluating the RTS,S candidate malaria vaccine

Sep 2005 – Aug 2010 **Health Economist**

Operation Hernia Foundation – Led two cost-effectiveness analyses of inguinal hernia repair in Ghana and Ecuador

Johns Hopkins University – Developed Monte Carlo Simulation for cost-effectiveness analysis, and contributed to economic modeling and publication writing on neonatal health trial evaluations.

World Health Organization – Led the design of an economic model to assess the cost-effectiveness of Rapid Diagnostic Tests for malaria and preparation of documents for publication http://www.wpro.who.int/sites/rdt/Assessing+RDT+Cost-Effectiveness.htm

Feb 2003 – Sep 2005 **London School of Hygiene and Tropical Medicine, London, UK**

Research Fellow: October 2003 – September 2005
Consultant: February 2003 – October 2003

Copenhagen Consensus – Challenge paper on communicable diseases – modeled the cost-benefit of scaling up coverage of malaria, HIV/AIDS, and basic health interventions in the developing world, and jointly wrote the report.
http://www.copenhagenconsensus.com/Default.aspx?ID=220

Economics of treatment of malaria in sub-Saharan Africa – Conducted probabilistic sensitivity analyses, expected value of information analyses, and collaborated on economic modeling and writing of academic papers and reports.

Rapid Costing Inputs Paper for UK Treasury on Increasing Development Assistance for Health Services – Updated estimates on the return to investing in health made in the Commission on Macroeconomics and Health Working Group 5 to inform investment of funds allocated at the G8 Summit

Jun 2002 – Oct 2003 **Oxford University, Health Economics Research Centre, Oxford, UK**

Research Assistant
The cost-effectiveness of screening for hereditary hemochromatosis – A decision analytic model assessing four alternatives for population screening for Hereditary Hemochromatosis
Making difficult decisions – A league table to assess the efficiency of medical practice in Oxfordshire UK
Priorities forum – member – an advisory board to the Oxfordshire Health Authority to assess complex decisions and to advise on issues requiring value judgments
Courses attended: Introduction to Health Economics, HERC, Oxford University
Advanced methods of Cost-Effectiveness Analysis, HERC, Oxford University
Ethical Issues in Medical Research, ETHOX, Oxford University

Education

Aug 2010 – Aug 2014 **Johns Hopkins Bloomberg School of Public Health, Department of International Health, Baltimore MD**

Doctor of Philosophy: Health Systems. Courses included epidemiology, biostatistics, health systems, international health, managing health services organizations, health economics, economic evaluation, design and conduct of community trials, comparative evaluation of health policy, summary measures of population health, health financing, public health and the law, health policy, microeconomics, humanitarian emergencies, budgeting and financial management, global burden of injuries, maternal and neonatal mortality
Dissertation Title: Economic evaluation of the costs and cost-effectiveness of the Diarrhea Alleviation Through Zinc and Oral Rehydration Therapy Program at scale in Gujarat India
Advisors: Prof. Richard Morrow, Prof. Alan Sorkin, and Dr. Amnesty Lefevre

Sep 2002 – Oct 2003 **City University, Department of Economics, London, UK**

Master of Science: Economic Evaluation in Health Care (with Distinction). Courses included healthcare economics, economic evaluation, epidemiology, clinical trials and survival analysis, needs assessment and quality of life, welfare economics, statistical methods for applied research, and computing skills workshops.
Dissertation Title: Dimensions in cost-effectiveness and expected value of information analysis
Advisors: Prof. Nancy Devlin and Prof. David Parkin

Sep 2000 – Oct 2001 **Oxford University, Institute of Biological Anthropology, Keble College; Oxford, UK**

Master of Science: Human Biology. Courses included an intensive study of human genetics, nutrition, developmental biology, human ecology and paleoanthropology. Specific papers of interest discussed: health and social inequality, health and ethnicity, and predicting diseases of importance for the next 20 years.
Dissertation Title: The Cost-Effectiveness of Screening for the C282Y Mutation in European Populations
Advisor: Prof. Ryk Ward

Jun 1997 – Aug 2000 **University of Georgia, Franklin School of Arts and Sciences, Athens, Georgia, USA**

Bachelor of Science (Hons): Cellular Biology. My course selection covered general biology, microbiology, neurobiology, endocrinology, immunology, biochemistry and genetics. Required core classes included general chemistry, organic chemistry, physics and calculus.
Bachelor of Arts: History (Hons). My course selection focused on American history, particularly in the Southern United States. Other topics included Caribbean, English, and European history. Required core classes included literature, psychology, philosophy and French language.
Studied for these degrees simultaneously.
Dissertation Title: An American Apocalypse: To what extent did disease contribute to the conquest of the Incan Empire?
Advisor: Prof. Thomas Whigham

Teaching and seminars

Johns Hopkins Bloomberg School of Public Health

- May 23, 2007. Cost-effectiveness in low- and middle-income countries: A review of debates surrounding decision rules. Economic Evaluation Discussion Group
- May 13, 2008. Adaptation of acceptability curves: Probabilistic sensitivity analysis according to fixed parameters. Economic Evaluation II. Faculty: Damian Walker
- Mar 23, 2013. Forecasting burden of long-term disability from neonatal conditions: results from the Projahnmo I trial, Sylhet Bangladesh. Faculty: John Bridges

Publications

- Shillcutt SD, Kingsnorth AN. Commentary on: characterizing the global burden of surgical disease: a method to estimate inguinal hernia epidemiology in Ghana. World J Surg 2014; 38(4): 997-8
- Lefevre AE, Shillcutt SD, Waters HR, Haider S, El Arifeen S, Mannan I, Seraji, HR, Shah R, Darmstadt GL, Wall SN, Williams EK, Black RE, Santosham M, Baqui AH, Projahnmo Study Group. Economic evaluation of neonatal care packages in a cluster-randomized controlled trial in Sylhet Bangladesh. Bull WHO 2013;91(10):736-45.
- Shillcutt SD, Sanders DL, Butron-Vila M, Kingsnorth AN. Cost-effectiveness of inguinal hernia surgery in northwestern Ecuador. World J Surg 2013;37(1):32-41
- Shillcutt SD, Lefevre AE, Lee ACC, Baqui AH, Black RE, Darmstadt GL. Forecasting burden of long term disability from neonatal conditions: results from the Projahnmo I trial, Sylhet Bangladesh. Health Policy Plann 2013;28(4):435-52.
- Maire N, Shillcutt S, Walker D, Tediosi F, Smith T. Cost effectiveness of the introduction of a pre-erythrocytic malaria vaccine into the Expanded Program on Immunization in sub-Saharan Africa: analysis of uncertainties using a stochastic individual-based simulation model of *Plasmodium falciparum* malaria. Value Health 2011;14(8):1028-38
- Shillcutt SD, Clarke MG, Kingsnorth AN. Cost-effectiveness of groin hernia surgery in the western region of Ghana. Arch Surg 2010;145(10):954-61.
- Lefevre AE, Shillcutt SD, Saha SK, Ahmed ASMNU, Ahmed S, Chowdhury AMAK, Law P, Black R, Santosham M, Darmstadt GL. Cost-effectiveness of skin barrier enhancing emollients to prevent infection and death among preterm neonates in Bangladesh. Bull WHO 2010;8(2):104-12.
- Shillcutt SD, Walker DG, Goodman CA, Mills AJ. Cost effectiveness in low- and middle-income countries: A review of debates surrounding decision rules. Pharmacoeconomics 2009;27(11):903-17.
- Kingsnorth AN, Clarke MG, Shillcutt SD. Public health and policy issues of hernia surgery in Africa. World J Surg 2009;33(6):1188-93.
- Shillcutt SD, Morel CM, Coleman PG, Goodman CA, Mills AJ. The cost-effectiveness of malaria diagnosis in sub-Saharan Africa in an era of combination therapy. Bull WHO 2008;86:101-110.

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- Mills AJ, Shillcutt SD. Communicable Diseases. In: How to Spend $50 Billion to Make the World a Better Place ed. Lomborg, B. Cambridge: Cambridge University Press, 2005.
- Teklehaimanot, A. et al. Coming to Grips With Malaria in the New Millennium. United Nations Millennium Project. London: Earthscan (contributed global costs of malaria intervention), 2005.
- Coleman PG, Morel CM, Shillcutt SD, Goodman CA, Mills AJ. A threshold analysis of the cost-effectiveness of artemisinin-based combination therapies in sub-Saharan Africa. Am J Trop Med Hyg 2004;71(Suppl 2):196-204.
- Mills AJ, Shillcutt SD. Communicable Diseases. In: Global Crises, Global Solutions ed. Lomborg, B. Cambridge: Cambridge University Press, 2004. (reviewed in The Economist, June 5-11, 2004). www.copenhagenconsensus.com
- Coleman PG, Goodman CA, Mills AJ, Morel CM, Shillcutt SD, Yeung S. When is confirmed malaria diagnosis cost-effective? Letter to the BMJ, 2004. http://bmj.bmjjournals.com/cgi/eletters/328/7455/1511#68084
- Arrow K et al. Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance Washington D.C.: National Academies Press (contributing author) 2004.

To be submitted

- LeFevre AE, Shillcutt SD, Mirani M, Soofi S, Mohammad S, Black RE, Feroze A, Ali I, Bhutta Z, The Hala Economic Evaluation Study Group. Economic Evaluation of a Community-based Newborn Care Intervention Implemented in Sindh, Pakistan: A Cluster Randomized Controlled Trial. To be submitted.

Review activities

- American Journal of Tropical Medicine and Hygiene
- Applied Health Economics and Health Policy
- BMC Health Services Research
- Disease Control Priorities Project, 3rd edition
- Health Policy and Planning
- Lancet
- Pharmacoeconomics
- Tropical Medicine and International Health
- Value in Health

Presentations

- 36th Global Health Council: "New technologies + Proven strategies = Health communities" Washington DC, 26-23 May 2009 "Cost-effectiveness of skin barrier enhancing emollients to prevent infection and death among preterm neonates in Bangladesh. Oral presentation by Samuel Shillcutt
- 6th iHEA World Congress: "Cost-Effectiveness in Low- and Middle-Income Countries: A Review of the Debates Surrounding Decision Rules." Poster presentation by Damian Walker, and "Economic Assessment of a Community-Based Package of Maternal and Newborn Care Interventions in Rural Bangladesh: Exploration of Cost-Effectiveness and Financial Barriers to the Procurement of Care" Poster presentation by Amnesty Lefevre. Copenhagen Denmark, 8-11 July 2007.
- 5th iHEA World Congress: "What health services are 'essential' for developing countries? The influence of cost-effectiveness, burden of disease, and other factors on World Bank recommendations," Barcelona Spain, 10-13 July 2005. Oral presentation by Prof. David Parkin.

- 5th European Conference in Health Economics: "Adaptation of acceptability curves: probabilistic sensitivity analysis according to fixed parameters," London UK, September 8-11, 2004. Poster and oral presentation by Samuel Shillcutt.
- International Conference on Improving Use of Medicines: "Enhancing the rational use of antimalarials: the cost-effectiveness of rapid immunochromatographic dipsticks in sub-Saharan Africa," Bangkok Thailand, March 30 – April 2, 2004. Poster and oral presentation by Samuel Shillcutt.
- Institute of Medicine workshop on economic and epidemiologic modelling "The economics of new anti-malarial drugs," Oxford England, July 30-31, 2003. Oral presentation on expected value of information analysis by Samuel Shillcutt.

Computer Skills
Microsoft Office, Endnote, TreeAge, @Risk, VBA Excel (beginner), STATA, Lives Saved Tool

Language Skills
English (native), Spanish (high intermediate)

References

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